Continuum Modeling of Planar Cell Polarity

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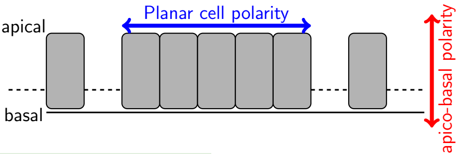
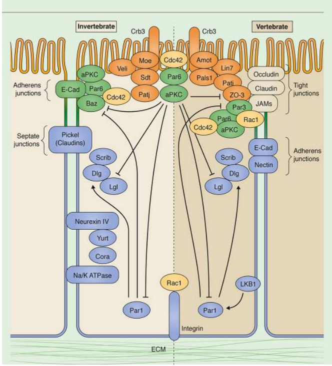
Cell polarity in tissues

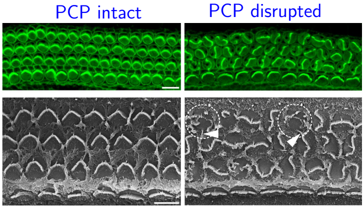




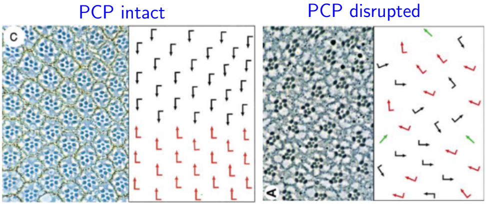
(Campanale et al., 2017. J. Cell Sci.)

- intrinsic asymmetry in cells- shape, structure, organization
- differential distribution of proteins → apico-basal polarity
- cell polarity is fundamental to several biological functions
- e.g. nutrient transport, cell adhesion, migration, etc.

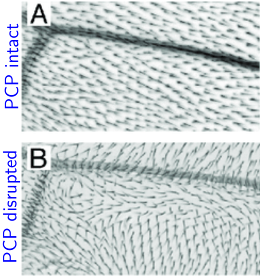
Planar cell polarity (PCP)



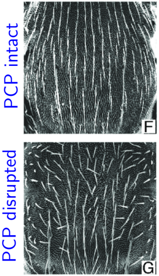
hair cells in mouse ear
(Siletti et al., 2017, PNAS)



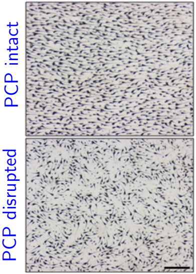
ommatidial arrangement in *Drosophila* eye
(Mlodzik, 2005, Adv. Dev. Bio.)



bristles in *Drosophila* wing
(Maung and Jenny, 2011, Organogenesis)



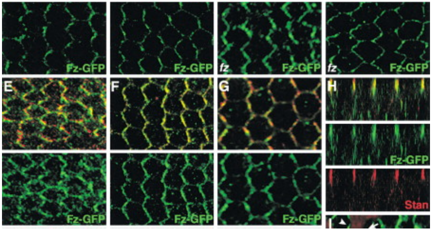
Drosophila thorax
(Maung and Jenny, 2011, Organogenesis)



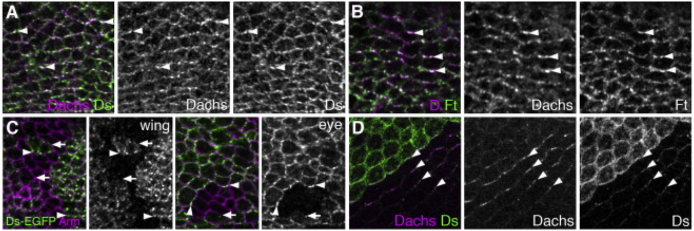
mouse skin hair
(Schnell and Carroll, 2014, Exp. Cell Res.)

Planar Cell Polarity (PCP)

Asymmetric localization of PCP proteins at the apical end of cell membrane



(Strutt, 2001, Molecular Cell)



(Brittle et al., 2012, Current Biology)

PCP: Core module

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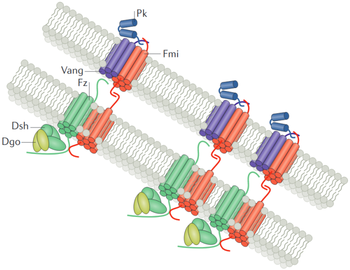
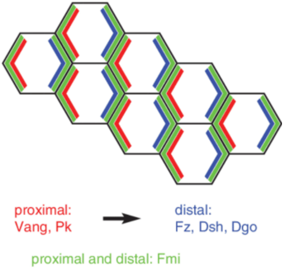
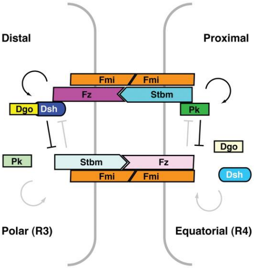


(Butler and Wallingford, 2017, Nat. Rev. Mol. Cell Bio.)

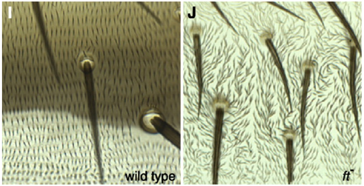


(Vladar et al., 2009, Cold Sp. Harb. Pers. Bio)



(Maung and Jenny, 2011, Organogenesis)

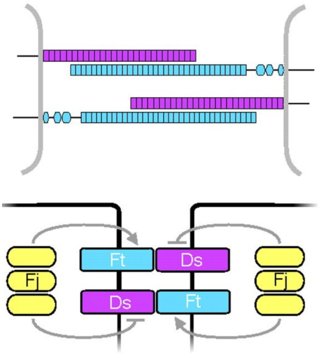
Cell polarity vs Tissue axis ?



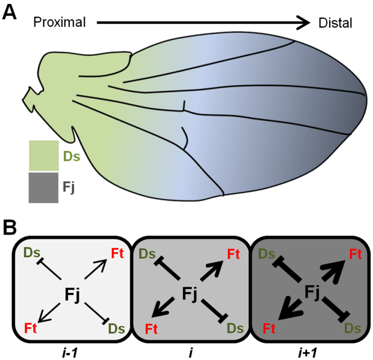
(Matakatsu and Blair, 2006, Development)

PCP: Global module

- **Ds** and **Ft**: atypical cadherins form heterodimers
- **Fj**: kinase



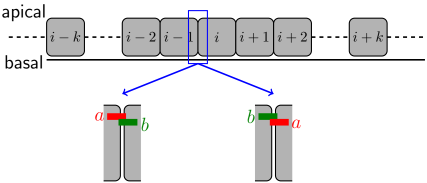
(Goodrich and Strutt, 2011, Development)



(Jolly et al., 2014, PLOS One)

These proteins are expressed in a tissue level gradient

One dimensional models



Dimers of opposing polarities

- Proteins/protein complexes from two neighboring cells form dimer across the cell membranes
- Intercellular protein interaction affect their detachment from cell membrane

$$\frac{da_i^L}{dt} = -k_{on} a_i^L b_{i-1}^R + k_{off} C_i^L + D_a \left(a_i^L - a_i^R\right)$$
$$\frac{da_i^R}{dt} = -k_{on} a_i^R b_{i+1}^L + k_{off} C_i^R + D_a \left(a_i^R - a_i^L\right)$$
$$\frac{dC_i^L}{dt} = k_{on} a_i^L b_{i-1}^R - k_{off} C_i^L$$

(Fisher and Strutt, 2019, Development)
(Fisher et al., 2017, Curr. Op. Sys. Bio.)

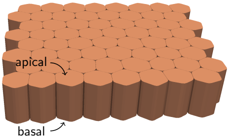
$$\frac{dC_{ij}}{dt} = k_{on} f_i d_j \left(1 + \alpha C_{ij}^m\right) - k_{off} C_{ij} \left(1 + \beta C_{ji}^m\right)$$

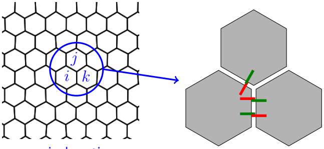
(Mani et al., 2013, PNAS)

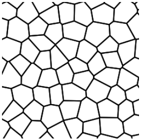
$$\frac{dFt_i^p}{dt} = \alpha_{Ft} Ft_i^u \mathcal{G}\left(Fj_i\right) - \beta_{Ft} Ft_i^p$$
$$\frac{dDs_i^p}{dt} = \alpha_{Ds} Ds_i^u \mathcal{G}\left(Fj_i\right) - \beta_{Ds} Ds_i^p$$
$$\frac{dC_{i,i+1}}{dt} = k_{on} \left(Ft_i^p Ds_{i+1}^u + Ds_i^u Ft_{i+1}^p\right) - k_{off} C_{i,i+1}$$

(Jolly et al., 2014, PLOS ONE)

Two dimensional models







$$\frac{\partial[Dsh]}{\partial t} = -P_1 - P_5^{\dagger} - P_8^{\dagger} + \mu_{Dsh}\nabla^2[Dsh]$$
$$P_1 = R_1[Dsh][Fz] - A_1B - \lambda_1[DshFz]$$
$$P_5 = R_5[Dsh]^{\dagger}[FzVang] - A_1^{\dagger}B^{\dagger}\lambda_5[DshFzVang]$$
$$\frac{\partial[Pk]}{\partial t} = -P_3 - P_7 - P_{10} + \mu_{Pk}\nabla^2[Pk]$$
$$P_3 = R_3[Vang][Pk] - \lambda_3[vangPk]$$
$$\vdots$$
$$\vdots$$
$$\frac{\partial[DshFzVangPk]}{\partial t} = P_8 + P_9 + P_{10} + \mu_{DshFzVangPk}\nabla^2[DshFzVangPk]$$
$$\vdots$$

($\sim$ 40 parameters)

(Amonlirdviman et al., 2005, Science)

$$\frac{dC_{ij}}{dt} = K\left(C_{ij};C_{ji}\right)a_1b_2 - K'C_{ij}$$
$$\frac{dC_{ji}}{dt} = K\left(C_{ji};C_{ij}\right)a_2b_1 - K'C_{ji}$$

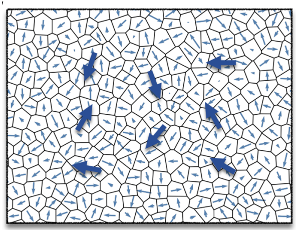
- Semi-phenomenological
- Stochastic effects

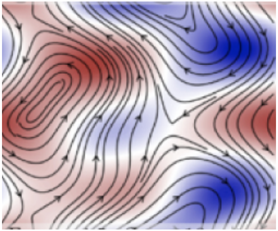
(Burak and Shraiman, 2009, PLOS Comp. Bio.)

$$\frac{dC_{12}}{dt} = \kappa f_1 g_2\left(1 + \alpha\mathcal{K}\left(C \to C_{12}\right)\right) - \gamma C_{12}\left(1 + \beta\mathcal{K}_d\left(\tilde{C} \dashv C_{12}\right)\right) + \eta(t) + \mathcal{M}e^{-t/\tau_m}$$

(Shadkhoo and Mani, 2020, PLOS Comp. Bio.)

PCP modeling

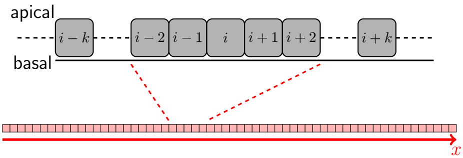




Discrete models ⟷ **Continuum models ?**

(Vicsek model) (Toner-Tu theory?)

Continuum modeling



$$a_L(i) \longmapsto a_L(x),\ \ a_R(i) \longmapsto a_R(x)$$
$$b_L(i) \longmapsto b_L(x),\ \ b_R(i) \longmapsto b_R(x)$$

$$\dot{a}_L(x) = \overbrace{\alpha\left(a_T(x) - a_L(x) - a_R(x)\right)}^{\text{attachment}} - \overbrace{\beta\left(1 + \gamma b_R(x-l)\right) a_L(x)}^{\text{detachment}}$$

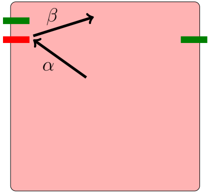
$$\dot{a}_R(x) = \alpha\left(a_T(x) - a_L(x) - a_R(x)\right) - \beta\left(1 + \gamma b_L(x+l)\right) a_R(x)$$

$$\dot{b}_L(x) = \alpha\left(b_T(x) - b_L(x) - b_R(x)\right) - \beta\left(1 + \gamma a_R(x-l)\right) b_L(x)$$

$$\dot{b}_R(x) = \alpha\left(b_T(x) - b_L(x) - b_R(x)\right) - \beta\left(1 + \gamma a_L(x+l)\right) b_R(x)$$

Assumptions

- No protein synthesis or degradation
- Protein diffusion time scale is very small
- Cells are non-motile and fixed in shape
- PCP features of length scale $\gg$ cell length
- Two proteins/protein complexes a and b localize at cell membrane and form dimers between two cells
- Proteins in the cytoplasm freely attach to the cell membrane
- Rate of detachment of membrane bound protein depends on its interaction with neighboring cell



One dimensional model

$$\dot{a}_L(x) = \alpha\left(a_T(x) - a_L(x) - a_R(x)\right) - \beta\left(1 + \gamma b_R(x-l)\right) a_L(x)$$
$$= \alpha\left(a_T(x) - a_L(x) - a_R(x)\right) - \beta\left(1 + \gamma\left(b_R(x) - l\frac{\partial b_R}{\partial x} + \cdots\right)\right) a_L(x)$$

Define $a_0 = a_R + a_L$, $p_a = a_R - a_L$, $b_0 = b_R + b_L$ and $p_b = b_R - b_L$ and non-dimensionalize the equations by

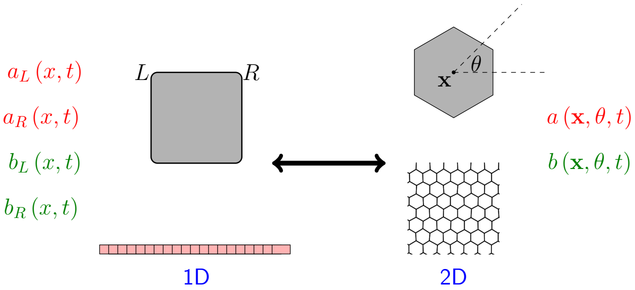
1. $\tau = 1/\beta$ for time
2. l for length
3. $1/\gamma$ for protein levels

to obtain

$$\dot{a}_0 = 2\alpha(a_T - a_0) - a_0 + \frac{1}{2}(a_0(b_0 - p_b') - p_a(p_b - b_0'))$$
$$\dot{b}_0 = 2\alpha(b_T - b_0) - b_0 + \frac{1}{2}(b_0(a_0 - p_a') - p_b(p_a - a_0'))$$
$$\dot{p}_a = -p_a + \frac{1}{2}(p_a(b_0 - p_b') + a_0(b_0' - p_b))$$
$$\dot{p}_b = -p_b + \frac{1}{2}(p_b(a_0 - p_a') + b_0(a_0' - p_a))$$

where prime ($'$) denotes the derivative with respect to x.

Two dimensional model



$$\frac{\partial a(\mathbf{x},\theta,t)}{\partial t} = \overbrace{\alpha\left(a_T(\mathbf{x},\mathbf{t}) - \frac{1}{2\pi}\int a(\mathbf{x},\theta,t)d\theta\right)}^{\text{attachment}} - \overbrace{(1 - f\left(b(\mathbf{x}+\Delta\mathbf{x}_\theta,\theta+\pi,t)\right))\, a(\mathbf{x},\theta,t)}^{\text{detachment}} + \overbrace{\mathcal{D}_\theta \frac{\partial^2}{\partial\theta^2} a(\mathbf{x},\theta,t)}^{\text{diffusion}}$$

$$\frac{\partial b(\mathbf{x},\theta,t)}{\partial t} = \alpha\left(b_T(\mathbf{x},\mathbf{t}) - \frac{1}{2\pi}\int b(\mathbf{x},\theta,t)d\theta\right) - (1 - f\left(a(\mathbf{x}+\Delta\mathbf{x}_\theta,\theta+\pi,t)\right))\, b(\mathbf{x},\theta,t) + \mathcal{D}_\theta \frac{\partial^2}{\partial\theta^2} b(\mathbf{x},\theta,t)$$

Two dimensional model

$$\frac{\partial a(\mathbf{x},\theta,t)}{\partial t} = \alpha\left(a_T(\mathbf{x},\mathbf{t}) - \frac{1}{2\pi}\int a(\mathbf{x},\theta,t)d\theta\right) - \left(1 - f\left(b(\mathbf{x}+\Delta\mathbf{x}_\theta,\theta+\pi,t)\right)\right)a(\mathbf{x},\theta,t) + \mathcal{D}_\theta\frac{\partial^2}{\partial\theta^2}a(\mathbf{x},\theta,t)$$
$$\frac{\partial b(\mathbf{x},\theta,t)}{\partial t} = \alpha\left(b_T(\mathbf{x},\mathbf{t}) - \frac{1}{2\pi}\int b(\mathbf{x},\theta,t)d\theta\right) - \left(1 - f\left(a(\mathbf{x}+\Delta\mathbf{x}_\theta,\theta+\pi,t)\right)\right)b(\mathbf{x},\theta,t) + \mathcal{D}_\theta\frac{\partial^2}{\partial\theta^2}b(\mathbf{x},\theta,t)$$

We can substitute $a(\mathbf{x},\theta,t) = \sum_m a_i(\mathbf{x},t)e^{im\theta}$ and $b(\mathbf{x},\theta,t) = \sum_m b_i(\mathbf{x},t)e^{im\theta}$ and integrate the above equations to obtain

$$\dot{a}_i(\mathbf{x},t) = \cdots$$
$$\dot{b}_i(\mathbf{x},t) = \cdots$$

Identifying the first harmonics as the degree of asymmetric localizations of two proteins $\mathbf{P}_a$ and $\mathbf{P}_b$, we obtain

$$\dot{a}_0 = \alpha a_T + \mathbf{P}_a\cdot(\nabla b_0 - 2\mathbf{P}_b) - a_0\left(\nabla\cdot\mathbf{P}_b - b_0 + \alpha + 1\right) + \frac{2|\mathbf{P}_a|^2|\mathbf{P}_b|^2}{(4\mathcal{D}_\theta + 1 - a_0 - b_0)^2} + \frac{\left[\left(\nabla\mathbf{P}_b + \nabla\mathbf{P}_b^\mathsf{T} - (\nabla\cdot\mathbf{P}_b)\mathbf{I}\right)\mathbf{P}_b\right]\cdot\mathbf{P}_a}{4\mathcal{D}_\theta + 1 - a_0 - b_0}$$
$$\dot{b}_0 = \alpha b_T + \mathbf{P}_b\cdot(\nabla a_0 - 2\mathbf{P}_a) - b_0\left(\nabla\cdot\mathbf{P}_a - a_0 + \alpha + 1\right) + \frac{2|\mathbf{P}_a|^2|\mathbf{P}_b|^2}{(4\mathcal{D}_\theta + 1 - a_0 - b_0)^2} + \frac{\left[\left(\nabla\mathbf{P}_a + \nabla\mathbf{P}_a^\mathsf{T} - (\nabla\cdot\mathbf{P}_a)\mathbf{I}\right)\mathbf{P}_a\right]\cdot\mathbf{P}_b}{4\mathcal{D}_\theta + 1 - a_0 - b_0}$$

$$\begin{aligned}\dot{\mathbf{P}}_a = {} & -\mathcal{D}_\theta\mathbf{P}_a + \frac{1}{2}a_0\left(\nabla b_0 - 2\mathbf{P}_b\right) - \frac{1}{2}\left(\nabla\mathbf{P}_b + \nabla\mathbf{P}_b^\mathsf{T} + (\nabla\cdot\mathbf{P}_b)\mathbf{I}\right)\mathbf{P}_a - (1 - b_0)\,\mathbf{P}_a \\ & + \frac{2|\mathbf{P}_a|^2\mathbf{P}_b - 2|\mathbf{P}_b|^2\mathbf{P}_a + \left(\mathbf{P}_a\otimes\mathbf{P}_b + \mathbf{P}_b\otimes\mathbf{P}_a - (\mathbf{P}_a\cdot\mathbf{P}_b)\,\mathbf{I}\right)\nabla b_0}{2\left(4\mathcal{D}_\theta + 1 - a_0 - b_0\right)}\end{aligned}$$
$$\begin{aligned}\dot{\mathbf{P}}_b = {} & -\mathcal{D}_\theta\mathbf{P}_b + \frac{1}{2}b_0\left(\nabla a_0 - 2\mathbf{P}_a\right) - \frac{1}{2}\left(\nabla\mathbf{P}_a + \nabla\mathbf{P}_a^\mathsf{T} + (\nabla\cdot\mathbf{P}_a)\mathbf{I}\right)\mathbf{P}_b - (1 - a_0)\,\mathbf{P}_b \\ & + \frac{2|\mathbf{P}_b|^2\mathbf{P}_a - 2|\mathbf{P}_a|^2\mathbf{P}_b + \left(\mathbf{P}_a\otimes\mathbf{P}_b + \mathbf{P}_b\otimes\mathbf{P}_a - (\mathbf{P}_a\cdot\mathbf{P}_b)\,\mathbf{I}\right)\nabla a_0}{2\left(4\mathcal{D}_\theta + 1 - a_0 - b_0\right)}\end{aligned}$$

Uniform expression levels $a_T = b_T = \rho$

Case-1: Homogeneous solution

$$\dot{a}_0 = \alpha\rho + \mathbf{P}_a \cdot (\cancel{\nabla b_0} - 2\mathbf{P}_b) - a_0 \left(\cancel{\nabla \cdot \mathbf{P}_b} - b_0 + \alpha + 1\right) + \frac{2|\mathbf{P}_a|^2|\mathbf{P}_b|^2}{(4\mathcal{D}_\theta + 1 - a_0 - b_0)^2} + \frac{\left[\cancel{\left(\nabla\mathbf{P}_b + \nabla\mathbf{P}_b^\intercal - (\nabla\cdot\mathbf{P}_b)\mathbf{I}\right)}\,\mathbf{P}_b\right]\cdot\mathbf{P}_a}{4\mathcal{D}_\theta + 1 - a_0 - b_0}$$

$$\dot{\mathbf{P}}_a = -\mathcal{D}_\theta\mathbf{P}_a + \frac{1}{2}a_0\left(\cancel{\nabla b_0} - 2\mathbf{P}_b\right) - \frac{1}{2}\cancel{\left(\nabla\mathbf{P}_b + \nabla\mathbf{P}_b^\intercal + (\nabla\cdot\mathbf{P}_b)\mathbf{I}\right)\mathbf{P}_a} - (1 - b_0)\,\mathbf{P}_a + \frac{2|\mathbf{P}_a|^2\mathbf{P}_b - 2|\mathbf{P}_b|^2\mathbf{P}_a + \cancel{\left(\mathbf{P}_a\otimes\mathbf{P}_b + \mathbf{P}_b\otimes\mathbf{P}_a - (\mathbf{P}_a\cdot\mathbf{P}_b)\mathbf{I}\right)\nabla b_0}}{2\,(4\mathcal{D}_\theta + 1 - a_0 - b_0)}$$

$\cdots$ similarly for b_0 and $\mathbf{P}_b$. Setting $\langle\mathbf{P}\rangle = \mathbf{P}_a + \mathbf{P}_b$ and $\Delta\mathbf{P} = \mathbf{P}_a - \mathbf{P}_b$ gives

$$a_0 = b_0 = \rho_0$$

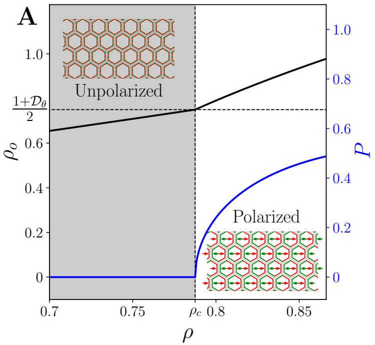
$$\langle\dot{\mathbf{P}}\rangle = -(1 + \mathcal{D}_\theta)\,\langle\mathbf{P}\rangle \implies \mathbf{P}_a = -\mathbf{P}_b = \mathbf{P}$$

$$\Delta\dot{\mathbf{P}} = -\left((\mathcal{D}_\theta + 1 - 2\rho_0)\,\mathbf{I} - \frac{2\left(\langle\mathbf{P}\rangle\otimes\langle\mathbf{P}\rangle\right) - \langle\mathbf{P}\rangle^2 - \Delta\mathbf{P}^2}{2(4\mathcal{D}_\theta + 1 - 2\rho_0)}\right)\Delta\mathbf{P}$$

$$P^2 = \begin{cases} 0, & \text{if } 2\rho_0 < 1 + \mathcal{D}_\theta \\ \dfrac{(2\rho_0 - 1 - \mathcal{D}_\theta)\,(4\mathcal{D}_\theta + 1 - 2\rho_0)}{2}, & \text{if } 2\rho_0 \geq 1 + \mathcal{D}_\theta. \end{cases}$$

super-critical pitchfork bifurcation

$$\rho_c = (1 + \mathcal{D}_\theta)\left(\frac{1}{2} + \frac{1 - \mathcal{D}_\theta}{4\alpha}\right)$$



Stability of homogeneous solution

We considered perturbations of type

$$a_0 = \rho_0 + \delta a_0 \exp\left(st + i\mathbf{q}\cdot\mathbf{r}\right), b_0 = \rho_0 + \delta b_0 \exp\left(st + i\mathbf{q}\cdot\mathbf{r}\right)$$

$$\mathbf{P}_a = \mathbf{P} + \delta\mathbf{P}_a \exp\left(st + i\mathbf{q}\cdot\mathbf{r}\right), \mathbf{P}_b = -\mathbf{P} + \delta\mathbf{P}_b \exp\left(st + i\mathbf{q}\cdot\mathbf{r}\right)$$

- *Stability of unpolarized state at* $\rho_0 \ll (1+\mathcal{D}_\theta)/2$*:* Roots of dispersion relation are $s = -1$, $-(\alpha+1)$, $-\left(1+\frac{\alpha}{2}\right) + 2\rho_0 \pm \frac{1}{2}\sqrt{\alpha^2 + 4\rho_0^2 q^2}$. $\Longrightarrow$ Stable

- *Stability of unpolarized state at* $\rho_0 = (1+\mathcal{D}_\theta)/2 - \varepsilon$ *where* $0 < \varepsilon \ll (1+\mathcal{D}_\theta)/2$*:* The dispersion relation

$$\mathcal{B}_1 s^4 + \mathcal{C}_1 s^3 + \mathcal{D}_1 s^2 + \mathcal{E}_1 s + \mathcal{F}_1 = 0. \quad (1)$$

Routh-Hurwitz stability criterion $\Longrightarrow$ Stable

- *Stability of polarized state at* $\rho_0 = (1+\mathcal{D}_\theta)/2 + \varepsilon$ *where* $0 < \varepsilon \ll 1$*:* The dispersion relation

$$\mathcal{A}_2 s^5 + \mathcal{B}_2 s^4 + \mathcal{C}_2 s^3 + \mathcal{D}_2 s^2 + \mathcal{E}_2 s + \mathcal{F}_2 = 0 \quad (2)$$

Numerical evaluation of roots $\Longrightarrow$ Unstable

Uniform expression levels $a_T = b_T = \rho$

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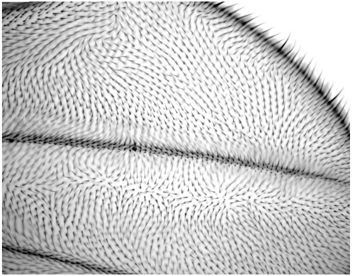
Case-2: Non-homogeneous solution

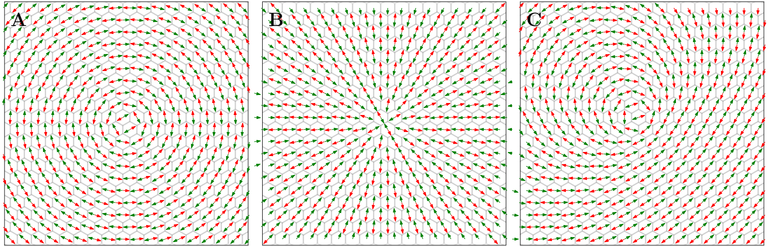
- $\rho > \rho_c$
- We assume very small deviation from perfectly opposing polarization
- If θ_a and θ_b are polarization directions then $\theta_a(\mathbf{x}) - \theta_b(\mathbf{x}) = \pi + \epsilon(\mathbf{x})$ with $|\epsilon| \sim 0$
- For $r \gg 1$ (in polar coordinates),

$$\sin(\phi - \theta_b)\left(\frac{\partial^2}{\partial \phi^2}\cos(\phi - \theta_b) + \cos(\phi - \theta_b)\right) = 0$$

$$\cos\theta_b(\mathbf{x})\frac{\partial \theta_b(\mathbf{x})}{\partial x} + \sin\theta_b(\mathbf{x})\frac{\partial \theta_b(\mathbf{x})}{\partial y} + \frac{2\epsilon(\mathbf{x})\rho_0}{P} = 0$$



(Axelrod, 2020, Curr. Op. Cell Bio.)



Gradient expressions

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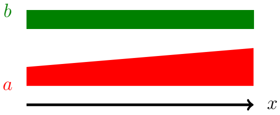
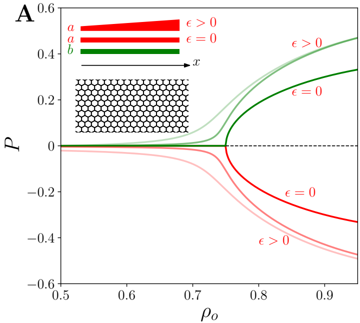
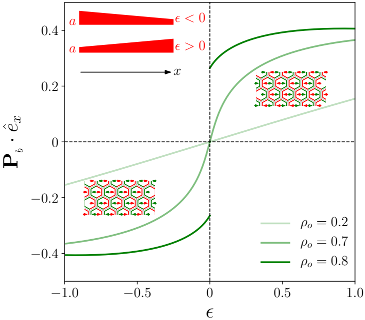
- protein b is expressed uniformly, $b_T = \rho$
- protein a is expressed in a shallow linear gradient such that $da/dx = \epsilon$ and $\epsilon \ll \rho/l$
- Consider solutions of type $a_0 = \rho_0 + a(x)$ and $b_0 = \rho_0 + b(x)$

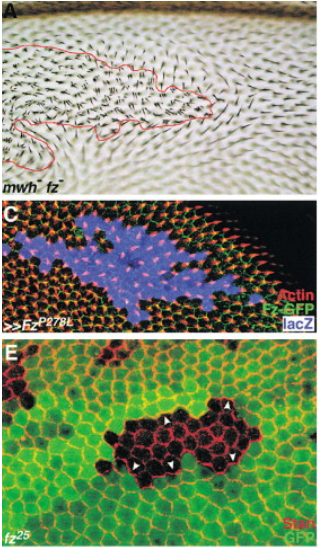




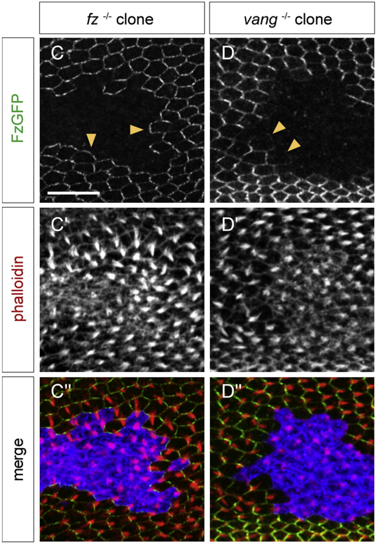


- Tissue is always polarized
- PCP direction is parallel to that of gradient
- **Stability:** Polarization remains stable even against non-uniform perturbations

Selective loss of a protein

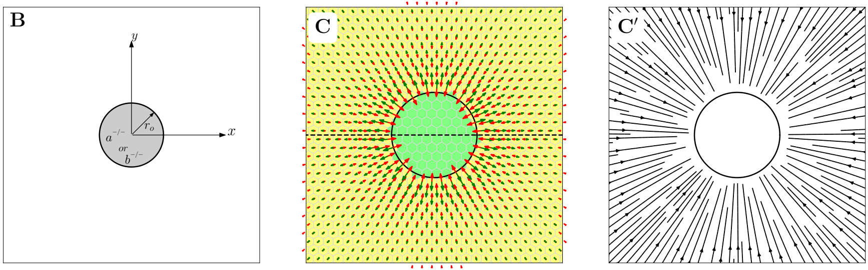


(Strutt, 2001, Molecular Cell)

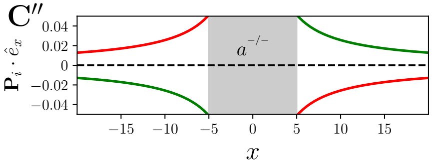


(Chen et al., 2008, Cell)

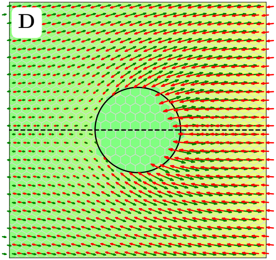
Selective loss of a protein

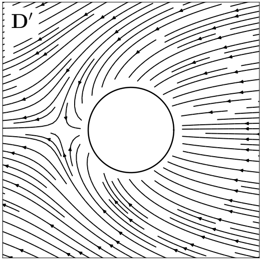


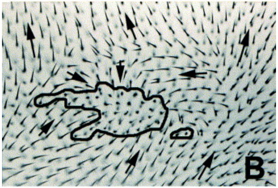
- $P \sim \mathcal{K}_1(x)$ where $\mathcal{K}_1(x)$ is the first order modified Bessel's function of second kind
- $\mathcal{K}_1(x)$ decays exponentially for large values of x

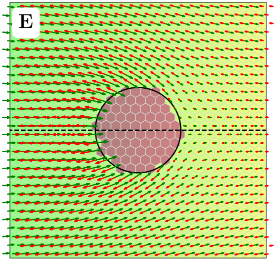


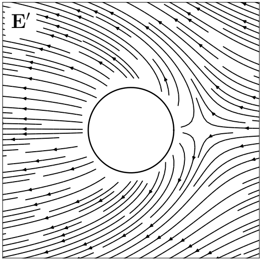
Selective loss of a protein

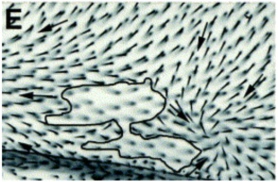












(Adler et al., 2000, Mech. of Dev.)