Filamentous actin dynamics

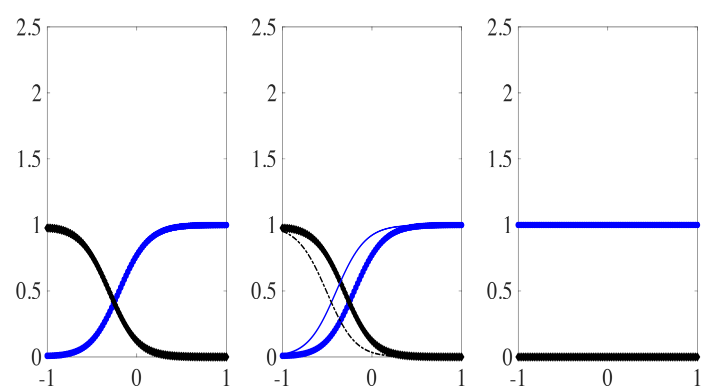
A(t): branched actin B(t): contractile/bundled actin

$$\frac{\partial A(x,t)}{\partial t} = A - A^2 - m_0 A\, B + D\Delta A$$

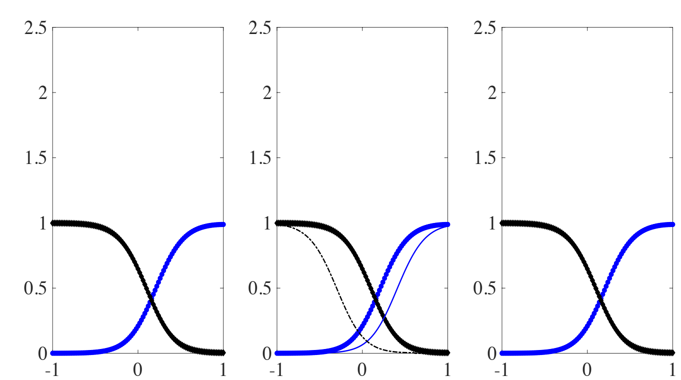
$$\frac{\partial B(x,t)}{\partial t} = B - B^2 - m_0 A\, B + D\Delta B$$

***Main observation*: quasi-stable polarized solution (stability improved in compartment model)**

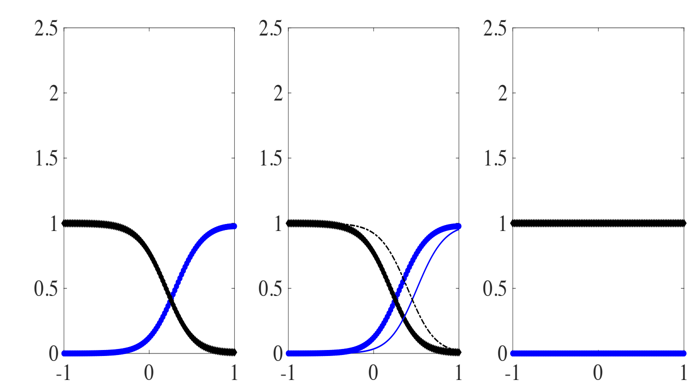
(a) branched actin wins



(b) temporary maintained



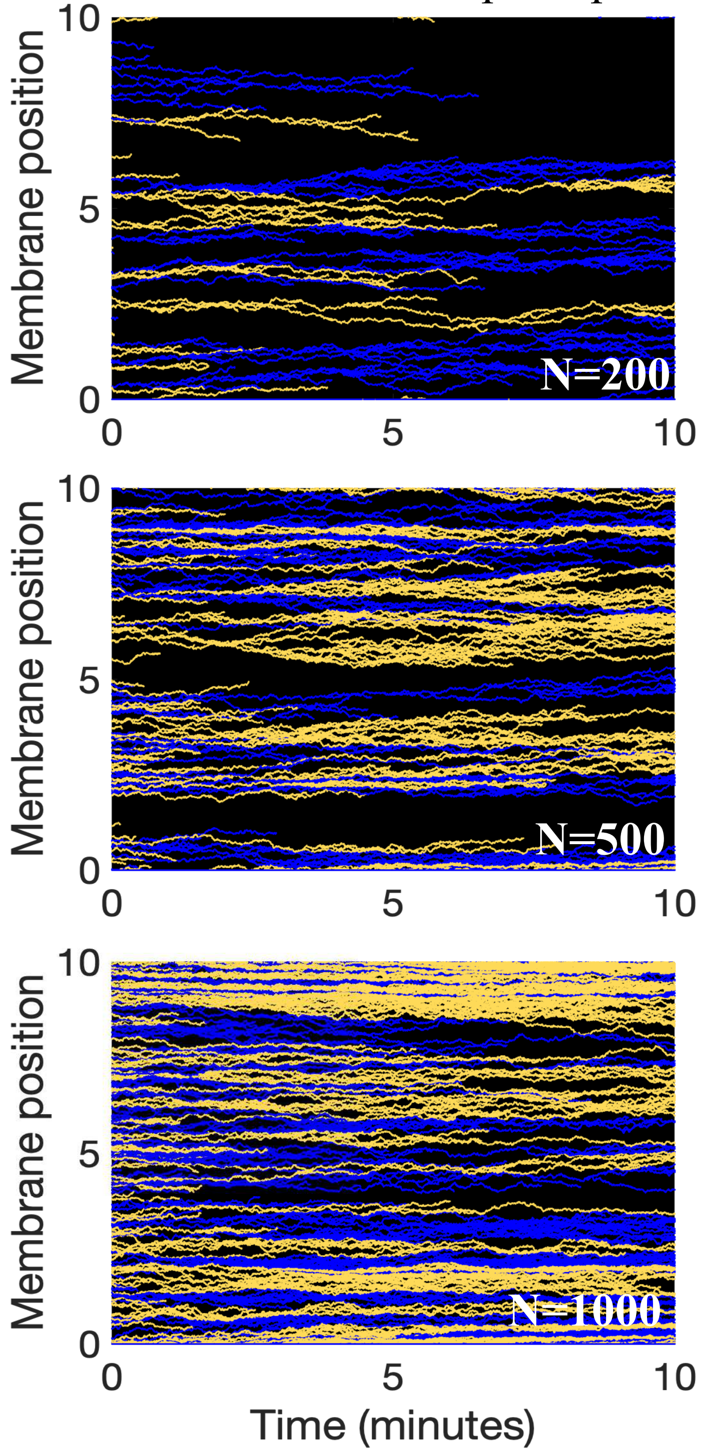
(c) contractile actin wins

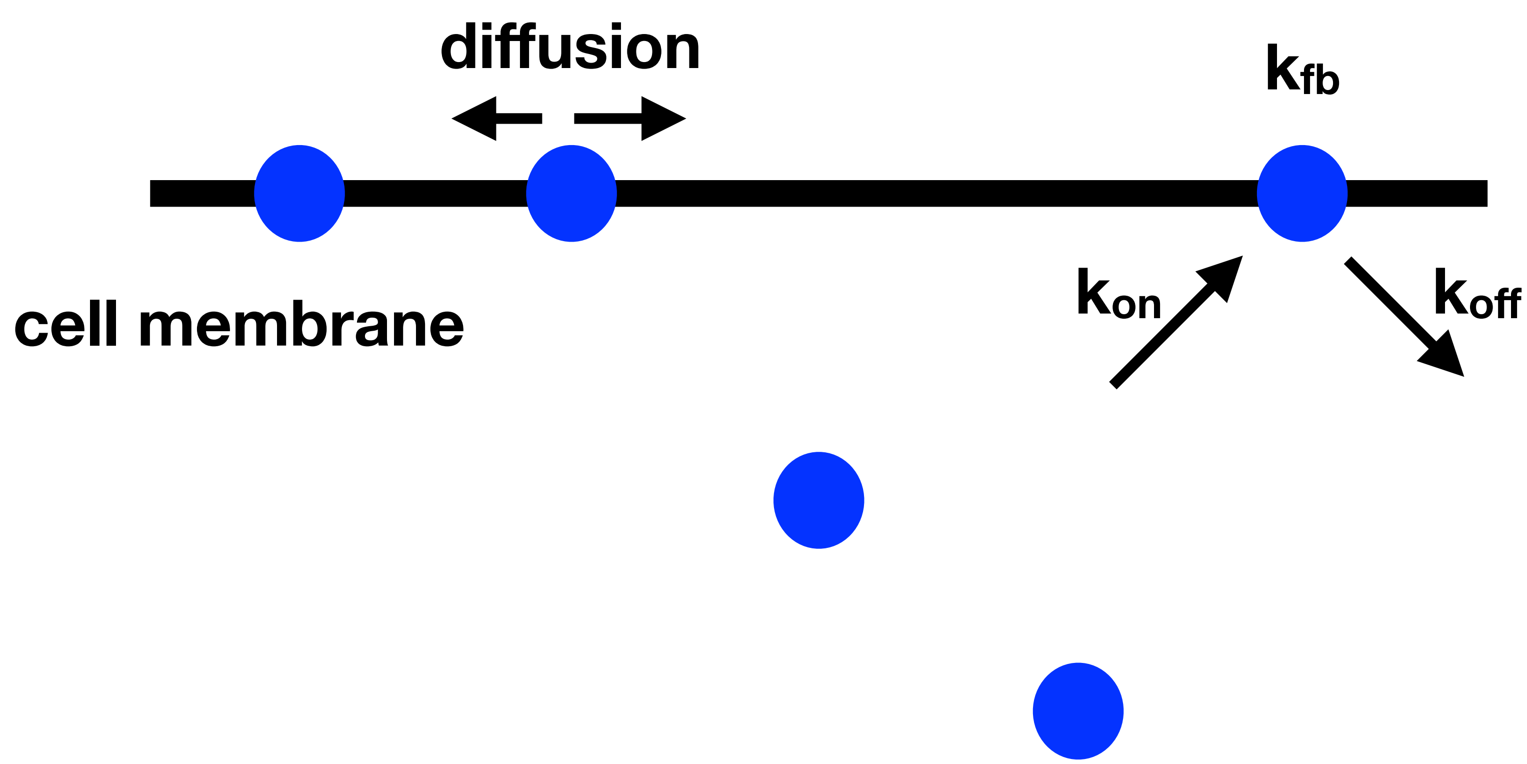


Polarity proteins

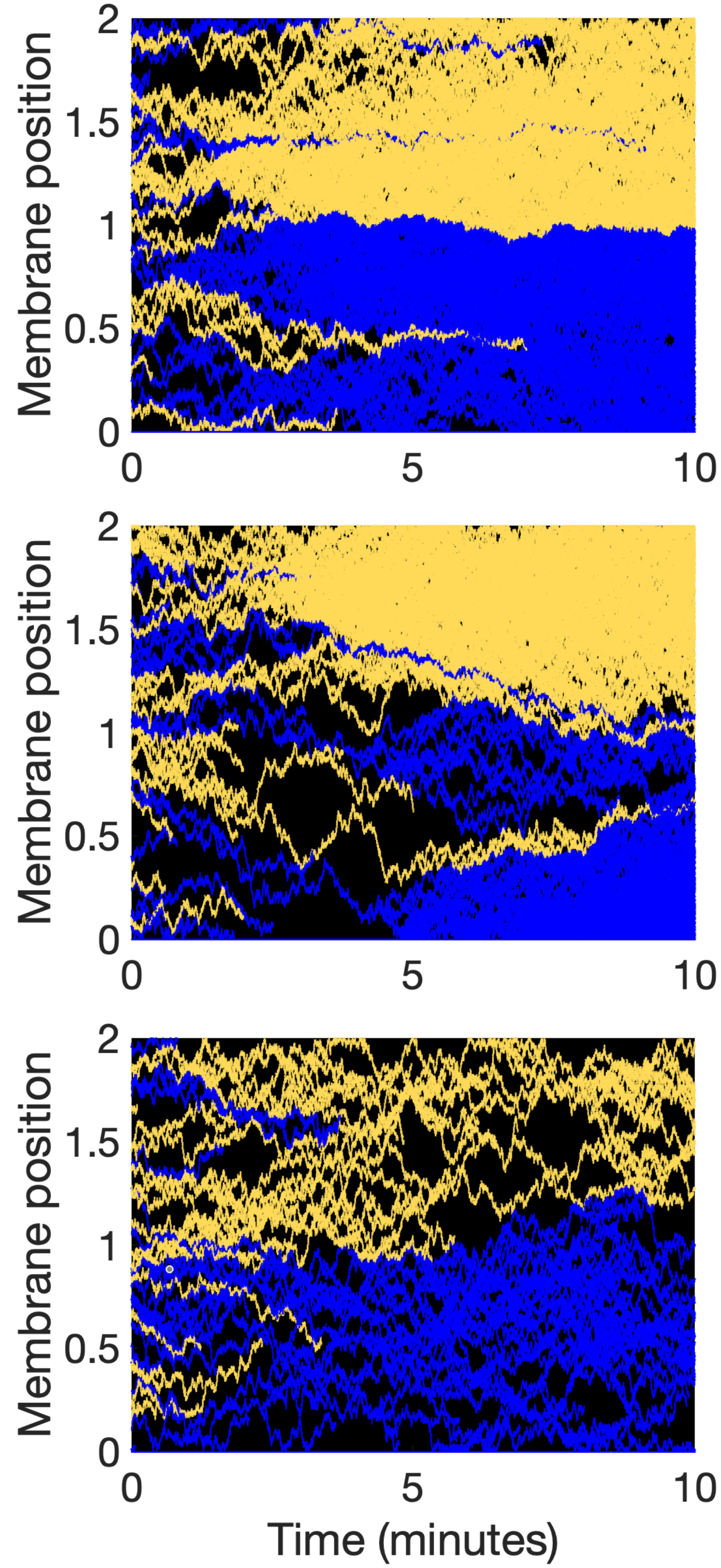
X(t): Rac Y(t): Rho

k_{on} = 0.001/min, k_{fb} = 1.0/min, k_{off} = 0.9/min
D = 0.012 um^2/min
2 types of molecules with exclusion principle and no jumping





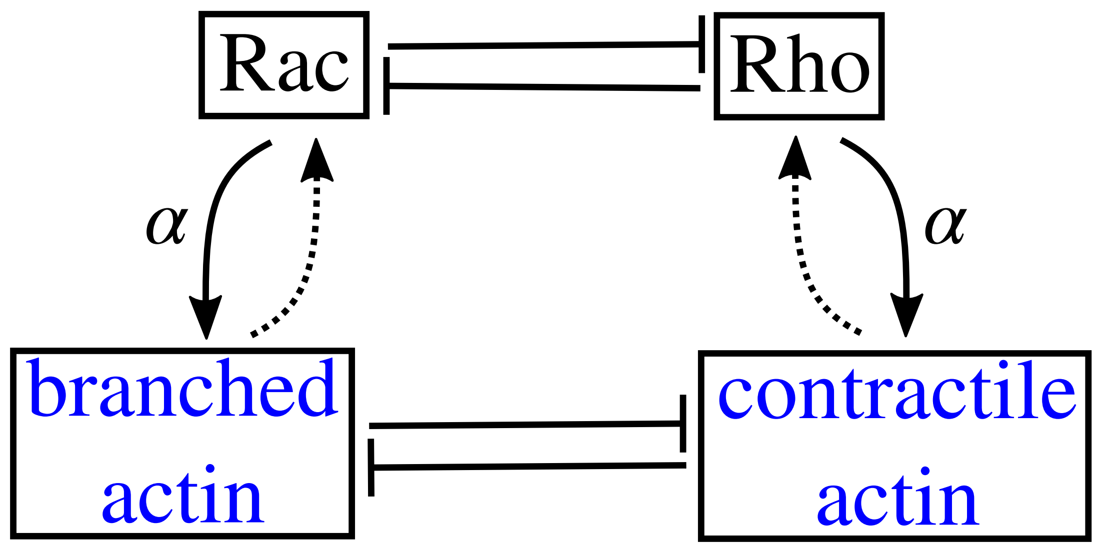
<u>Pre-check</u>: polarity dynamics with <u>prescribed</u> spatially-dependent rates for chemical reactions (k_{on}, k_{off}, k_{fb})



Coupling

A(t): branched actin **B(t): contractile/bundled actin**

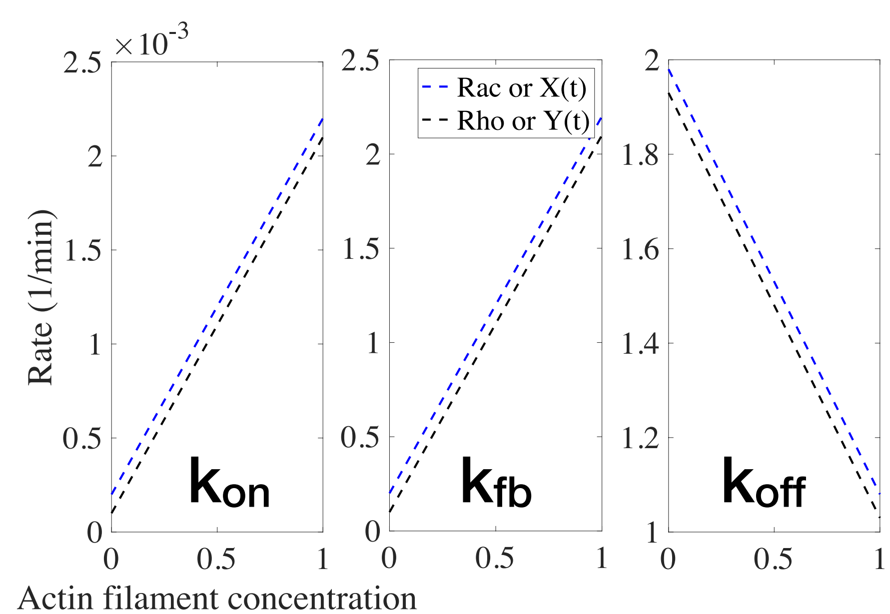
X(t): Rac **Y(t): Rho**



$$\frac{\partial A(x,t)}{\partial t} = (1 + \alpha X_{\textbf{interp}})A - A^2 - m_0 A\,B + D\Delta A$$

$$\frac{\partial B(x,t)}{\partial t} = (1 + \alpha Y_{\textbf{interp}})B - B^2 - m_0 A\,B + D\Delta B$$

Actin→Rho/Rac affects rates of chemical reactions: k_{on}, k_{fb}, k_{off}



Tests:

(1) Local perturbation from polarized solutions for actin filaments:

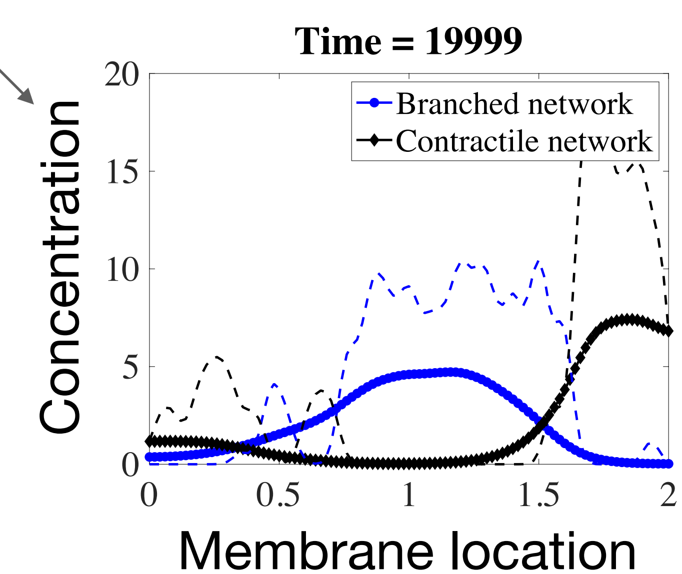
- The polarized solution is `recovered'

$\alpha = 0.5$	recovered
$\alpha = 0.2$	recovered
$\alpha = 0.1$	recovered

(2) Random initial distribution for actin filaments:

- The polarized solution is `recovered' depending on the strength of coupling

$\alpha = 0.5$	recovered 9** out of 10 simulations
$\alpha = 0.2$	recovered 9 out of 10 simulations
$\alpha = 0.1$	recovered 7 out of 10 simulations

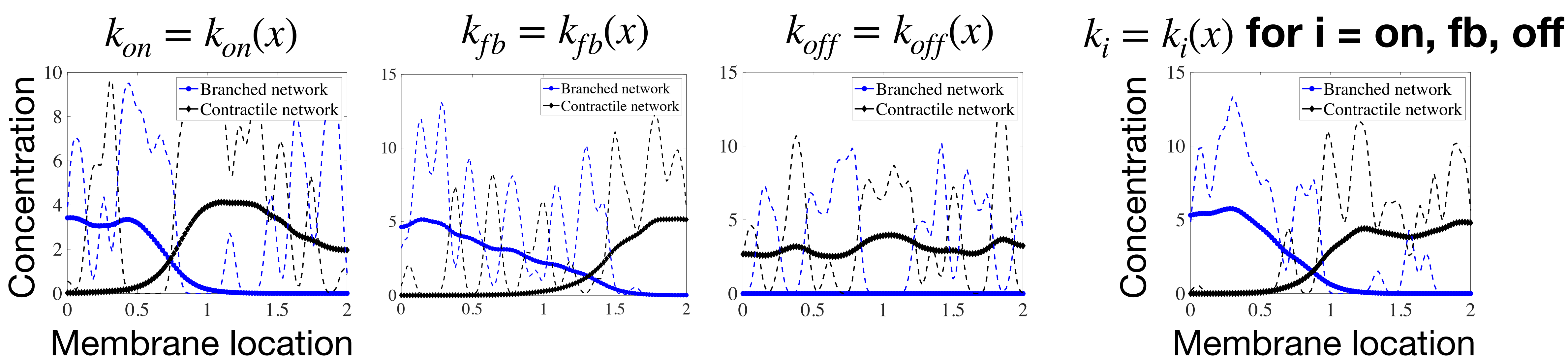


<u>Tests</u>:

(3) Do all chemical rates depend on actin filament concentration?

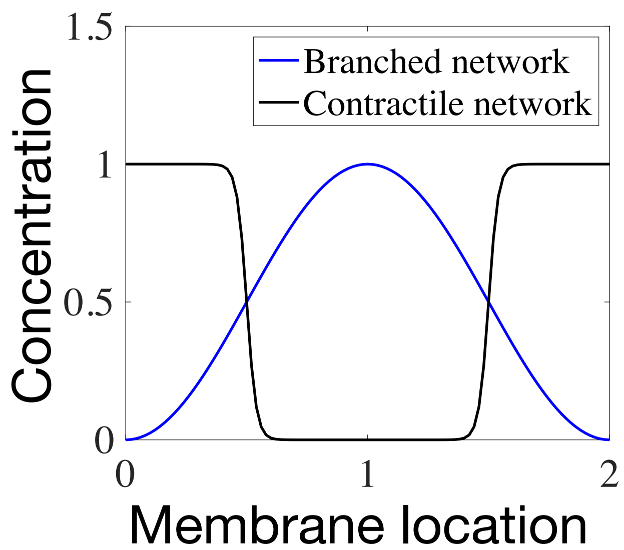
$\alpha = 0.5$

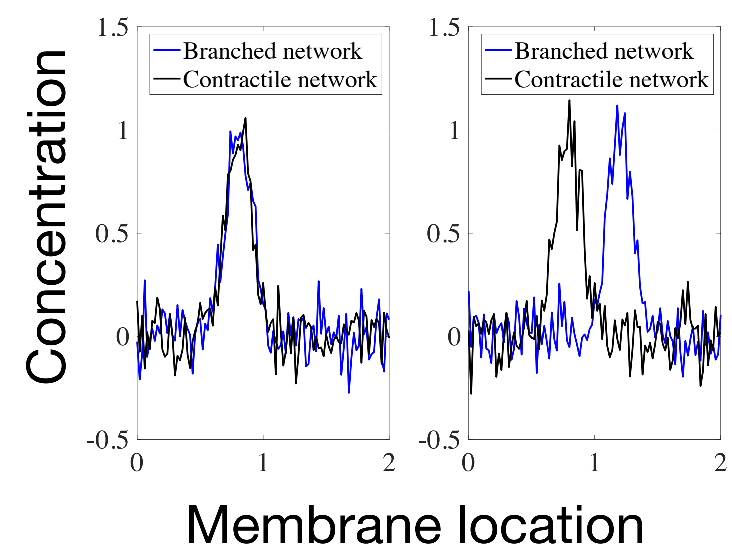
$k_{on} = k_{on}(x)$	recovered 4** out of 5 simulations
$k_{fb} = k_{fb}(x)$	recovered 5 out of 5 simulations
$k_{off} = k_{off}(x)$	recovered 3 out of 5 simulations



<u>Tests</u>:

(4) `Odd' initial distributions for the actin filaments:





$\alpha = 0.5$

recovered 10 out of 10 simulations

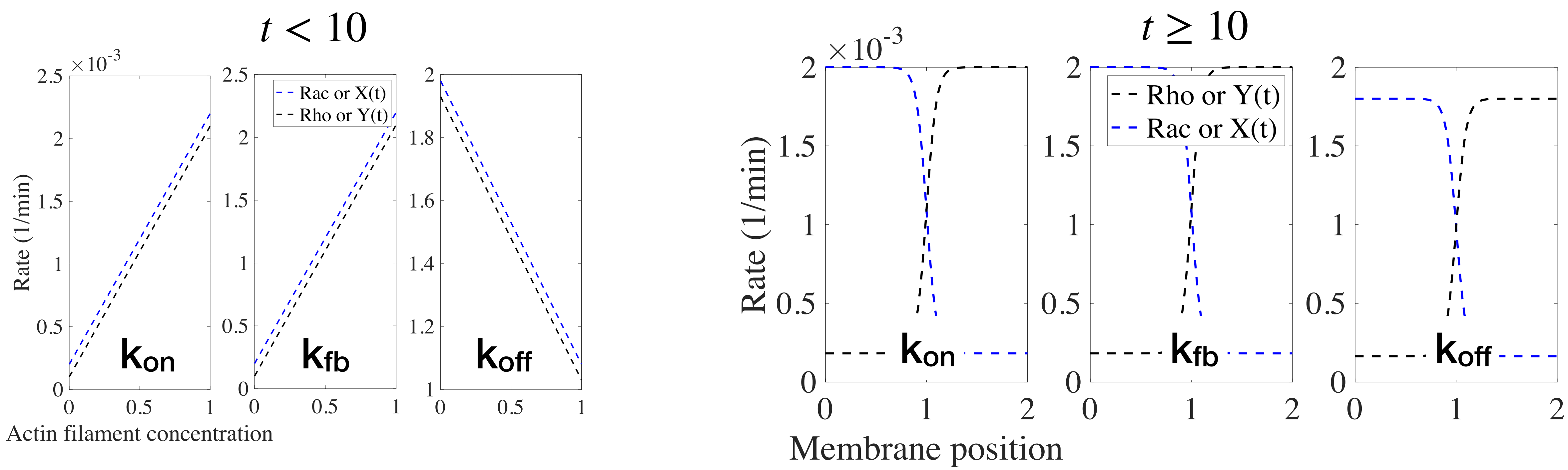
$\alpha = 0.5$

recovered 8 out of 10 simulations

Tests:

(5) Re-establishing polarization in `response' to external cues:

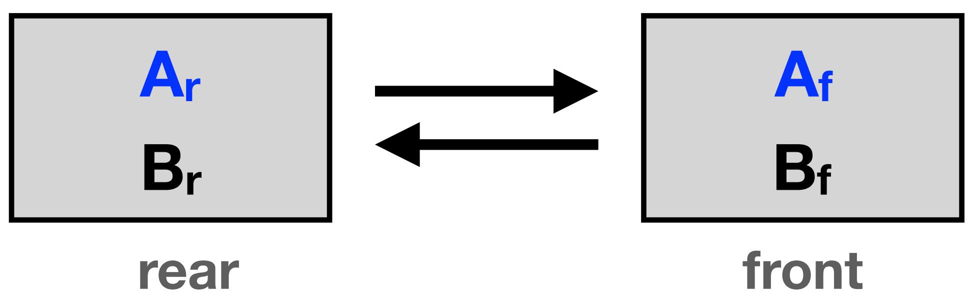
- Coupled feedback until t = 10, then prescribed spatial profile for the chemical rates for polarity proteins (as shown below)



- Unpolarized steady state (one actin species wins) in 9 out 10 simulations, while in 1 out 10 simulations, the re-polarized solution is stable.

Filamentous actin dynamics

$A_f(t)$: branched actin in front compartment
$A_r(t)$: branched actin in rear compartment
$B_f(t)$: bundled actin in front compartment
$B_r(t)$: bundled actin in front compartment

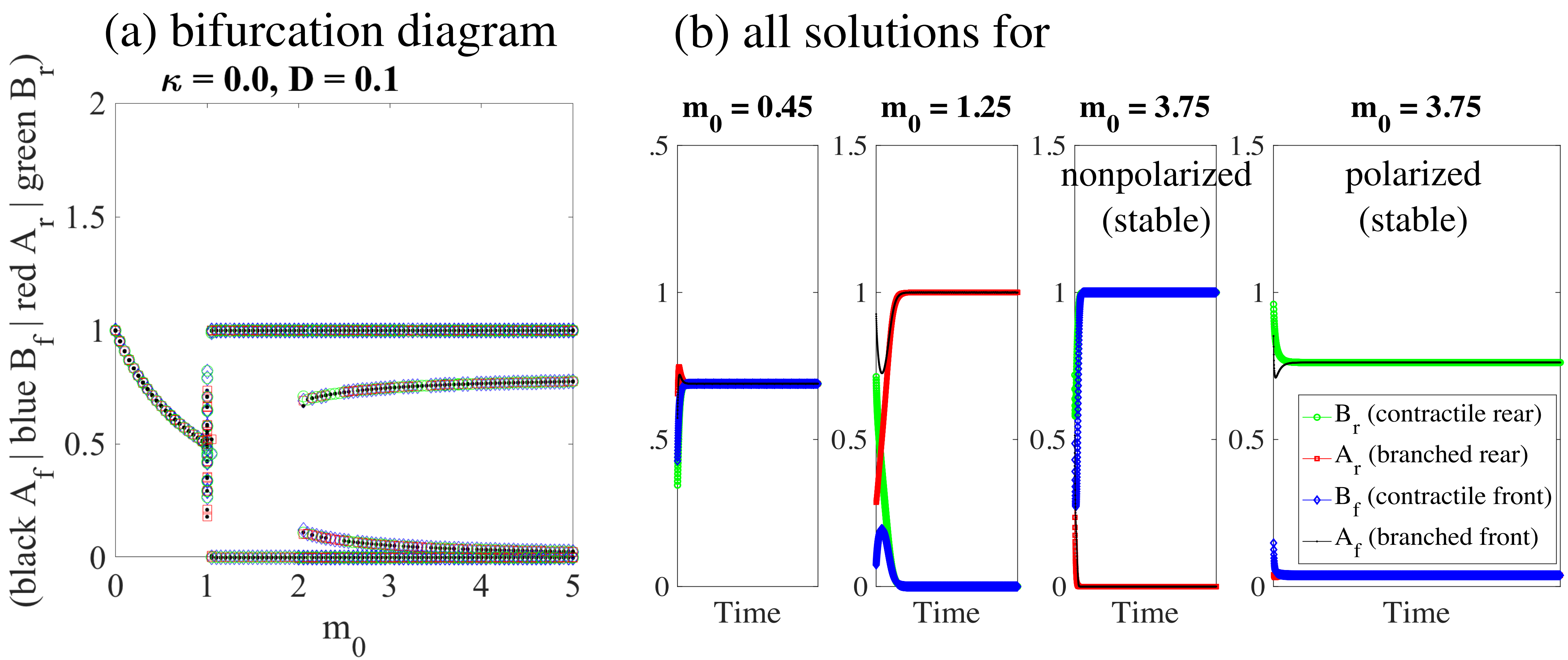


$$
\begin{aligned}
\frac{dA_f}{dt} &= A_f - A_f^2 - m_0 A_f B_f + D(A_r - A_f) = g_1(A_f, A_r, B_f)\\
\frac{dB_f}{dt} &= B_f - B_f^2 - m_0 A_f B_f + D(B_r - B_f) = g_2(A_f, A_r, B_f)\\
\frac{dA_r}{dt} &= A_r - A_r^2 - m_0 A_r B_r + D(A_f - A_r) = f_1(A_f, A_r, B_r)\\
\frac{dB_r}{dt} &= B_r - B_r^2 - m_0 A_r B_r + D(B_f - B_r) = f_2(A_f, A_r, B_f)
\end{aligned}
$$

diffusion

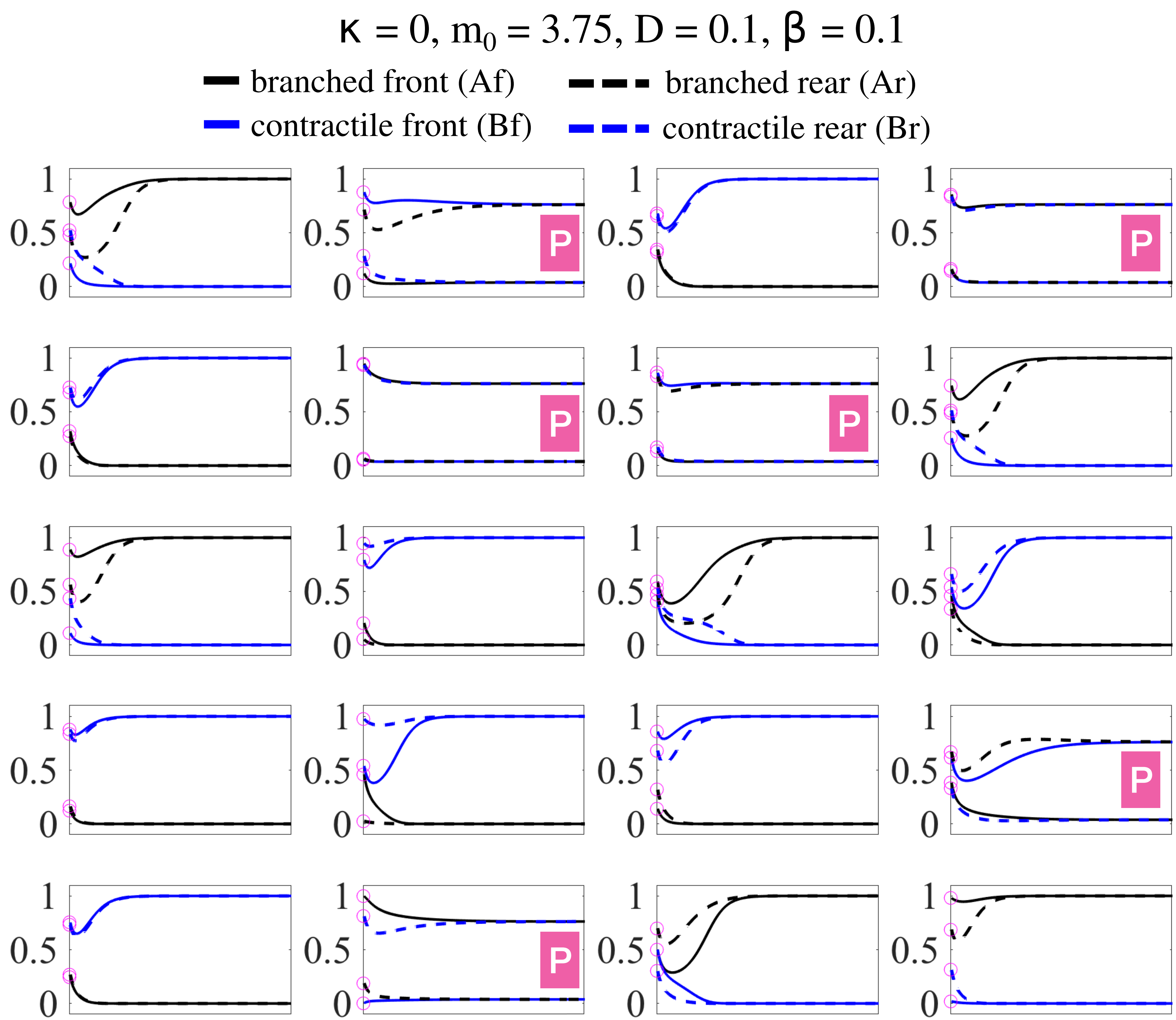
competition
(rate of predation)

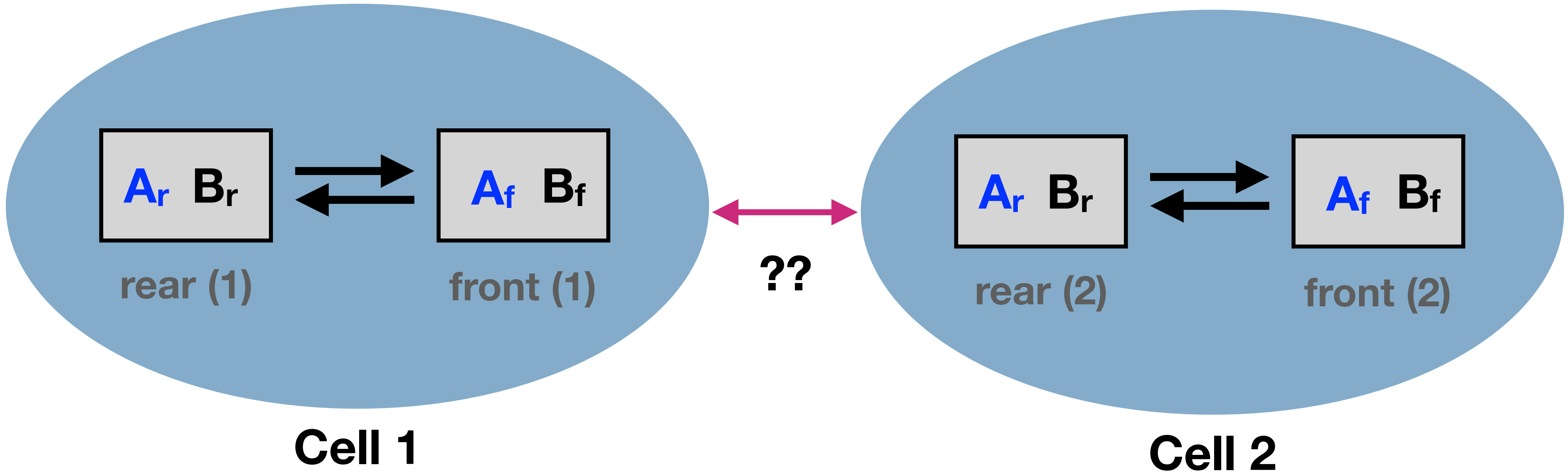
Depending on the competition term, polarized or non-polarized stable distribution emerge from random initial distribution



*only non-polarized states exist with high diffusion

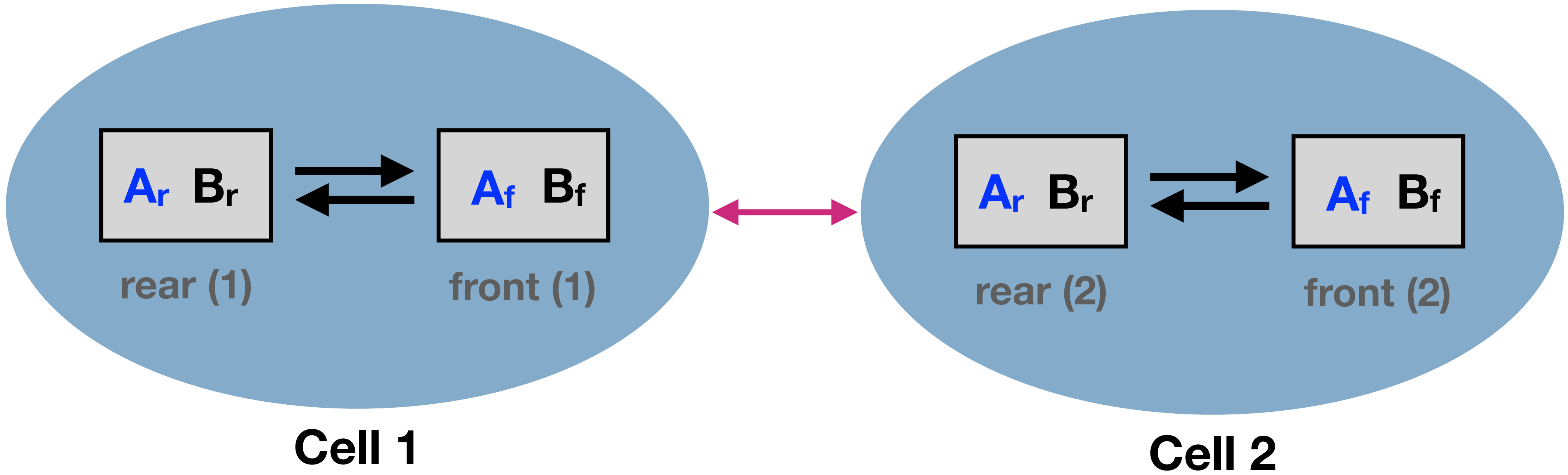
20 iterations with various initial conditions (P indicates polarized stable steady state solution)





Cell-cell coupling schemes (version 01):

- **No coupling**
- **Self-promotion: branched actin in (1) promotes branched actin in (2). Same for bundled actin.**
- **Self-inhibition**
- **Contact promotion**
- **Contact inhibition**
- **Cross promotion**
- **Cross inhibition**
- **Contact promotion & self-inhibition**
- **Contact inhibition & self-promotion**



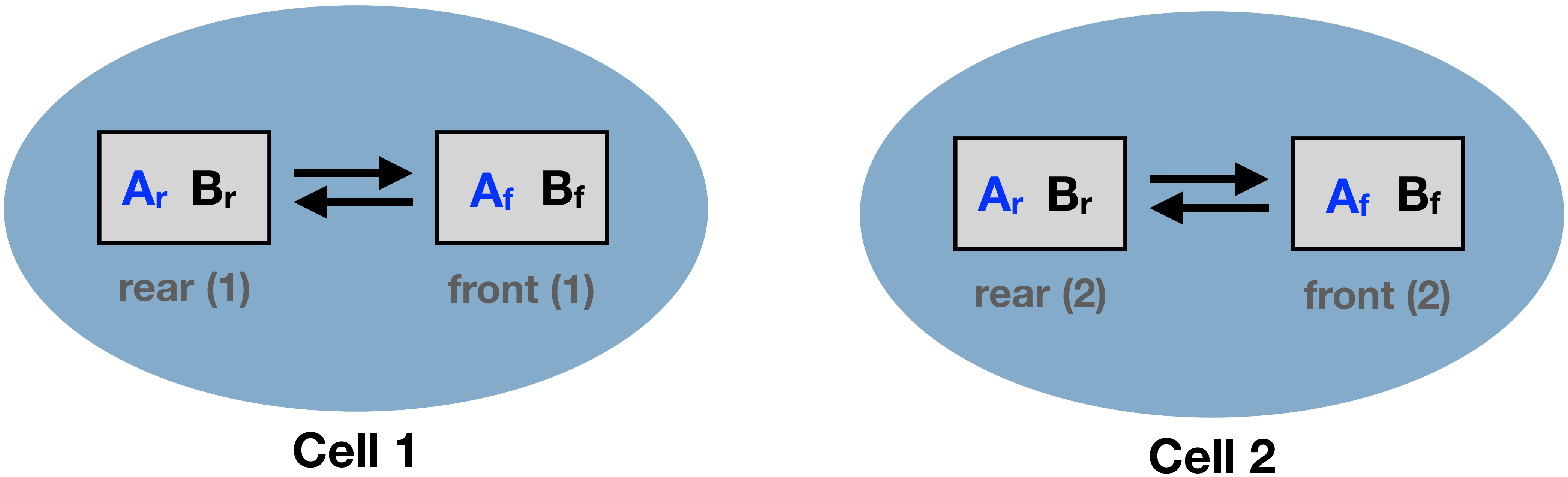
Cell 1

$$
\begin{aligned}
\frac{dA_{1,f}}{dt} &= [A_{1,f} + \boxed{\alpha A_{2,r} + \beta B_{2,r}}] - A_{1,f}^2 - m_0 A_{1,f} B_{1,f} + D(A_{1,r} - A_{1,f}) \\
\frac{dB_{1,f}}{dt} &= [B_{1,f} + \boxed{\gamma A_{2,r} + \delta B_{2,r}}] - B_{1,f}^2 - m_0 A_{1,f} B_{1,f} + D(B_{1,r} - B_{1,f}) \\
\frac{dA_{1,r}}{dt} &= A_{1,r} - A_{1,r}^2 - m_0 A_{1,r} B_{1,r} + D(A_{1,f} - A_{1,r}) \\
\frac{dB_{1,r}}{dt} &= B_{1,r} - B_{1,r}^2 - m_0 A_{1,r} B_{1,r} + D(B_{1,f} - B_{1,r}).
\end{aligned}
$$

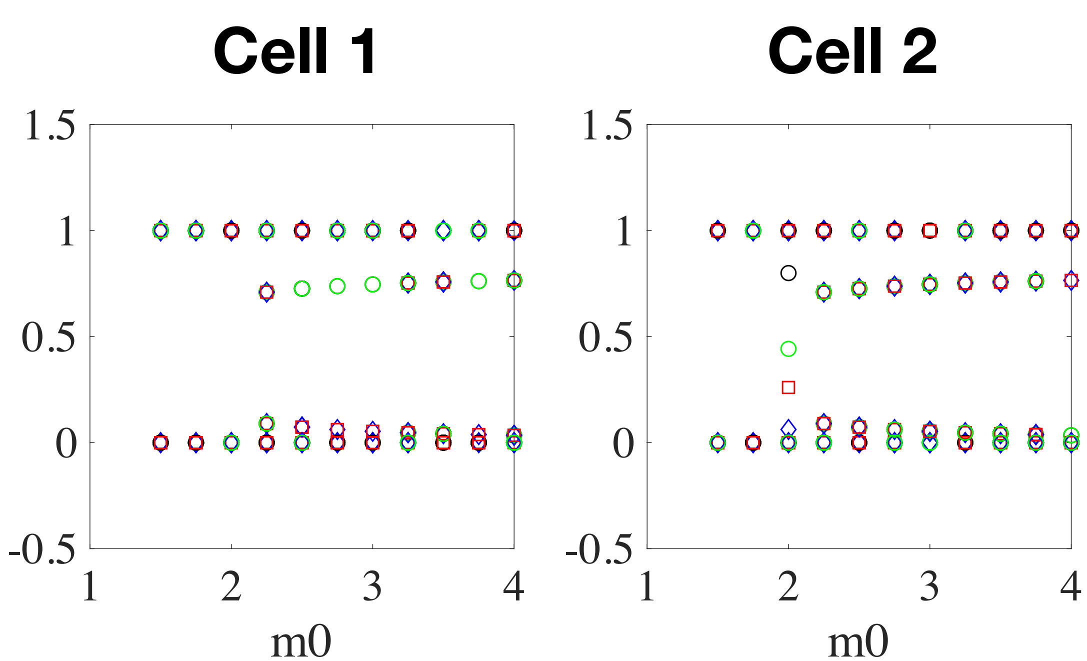
Cell 2

$$
\begin{aligned}
\frac{dA_{2,f}}{dt} &= A_{2,f} - A_{2,f}^2 - m_0 A_{2,f} B_{2,f} + D(A_{2,r} - A_{2,f}) \\
\frac{dB_{2,f}}{dt} &= B_{2,f} - B_{2,f}^2 - m_0 A_{2,f} B_{2,f} + D(B_{2,r} - B_{2,f}) \\
\frac{dA_{2,r}}{dt} &= [A_{2,r} + \boxed{\alpha A_{1,f} + \beta B_{1,f}}] - A_{2,r}^2 - m_0 A_{2,r} B_{2,r} + D(A_{2,f} - A_{2,r}) \\
\frac{dB_{2,r}}{dt} &= [B_{2,r} + \boxed{\gamma A_{1,f} + \delta B_{1,f}}] - B_{2,r}^2 - m_0 A_{2,r} B_{2,r} + D(B_{2,f} - B_{2,r}).
\end{aligned}
$$

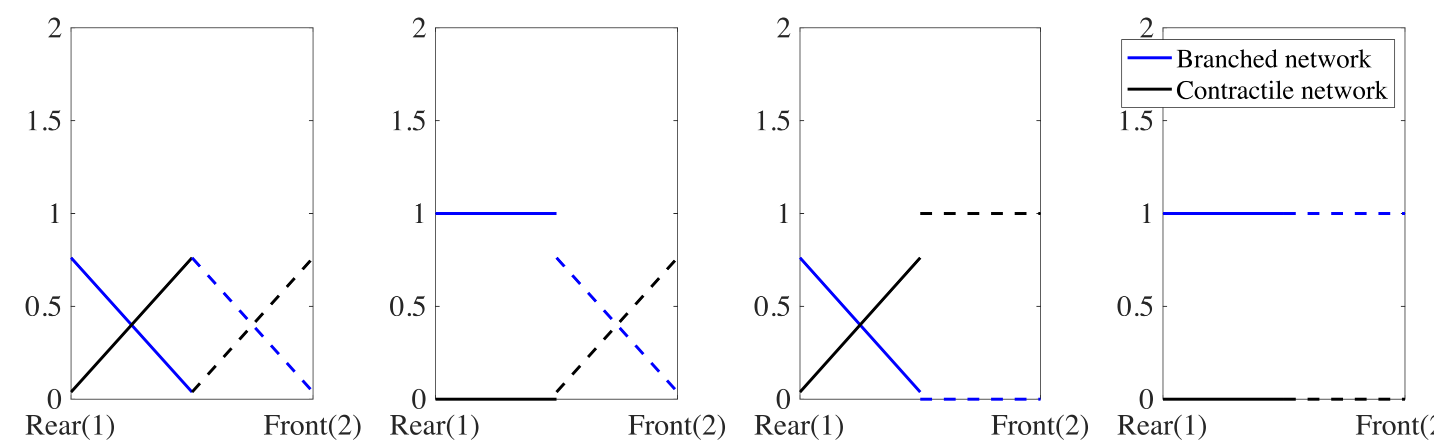
No
cell-cell coupling



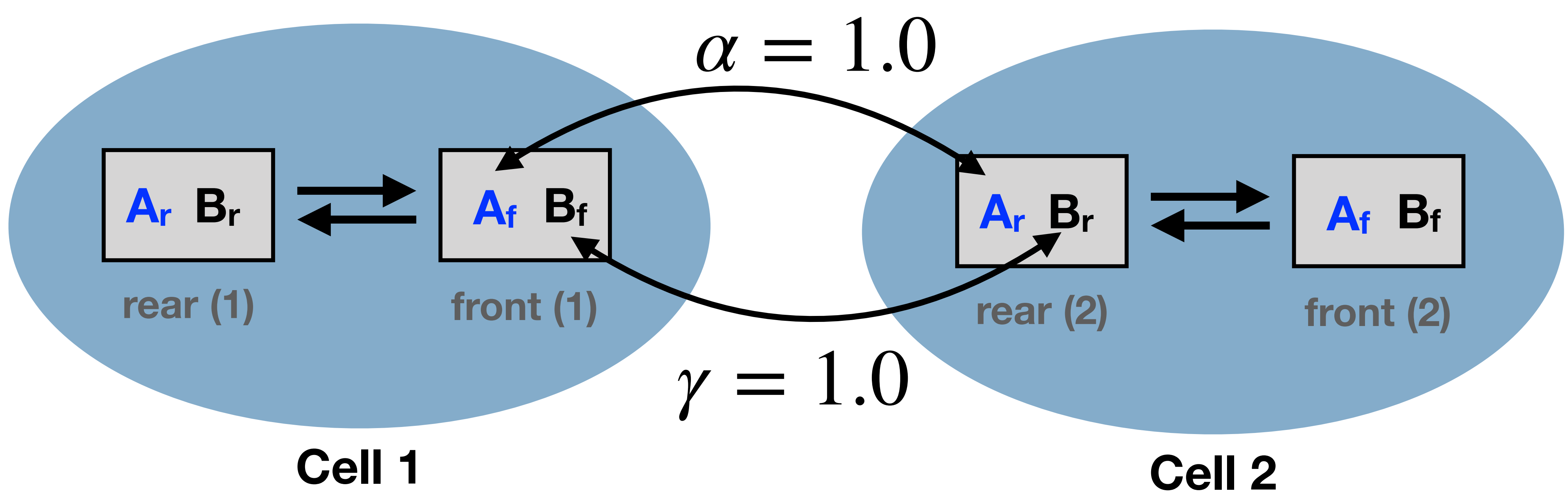
$D = 0.1$, $\alpha = 0$, $\beta = 0$, $\gamma = 0$, $\delta = 0$

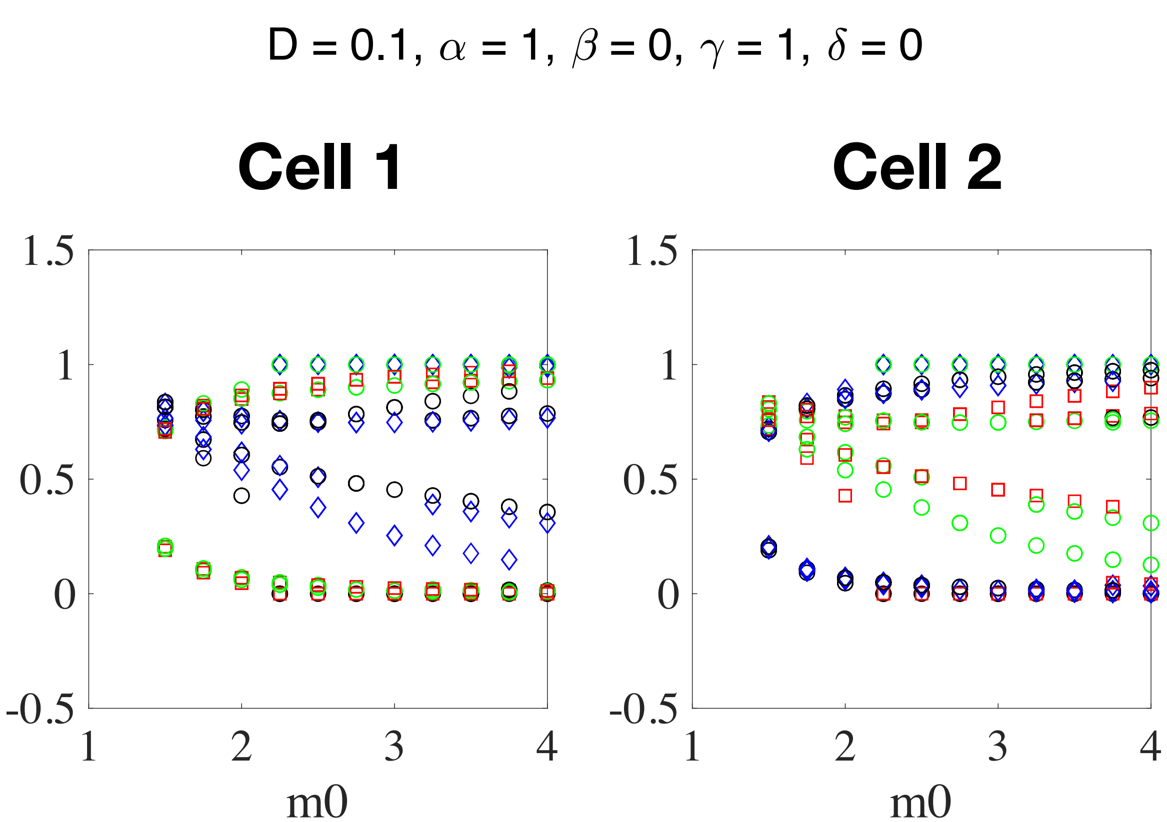


Emergent distributions of actin networks in both cells

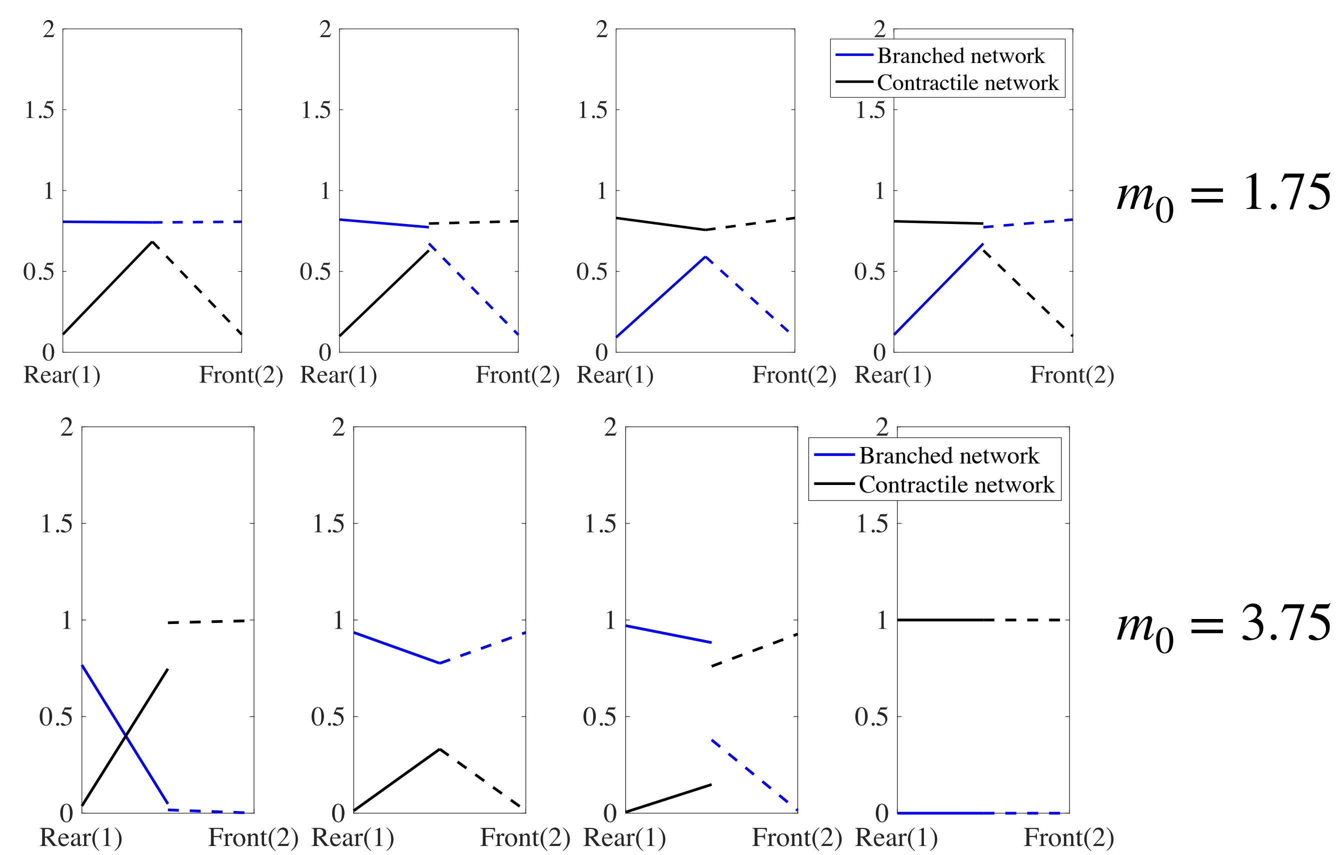


Self-promotion cell-cell coupling

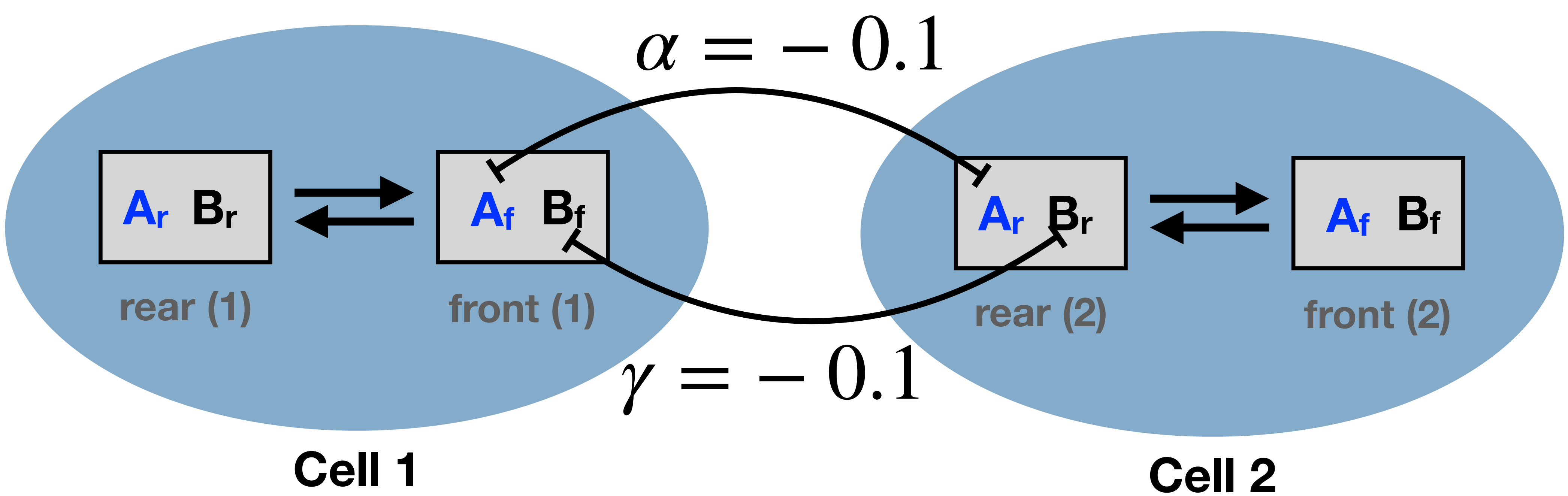




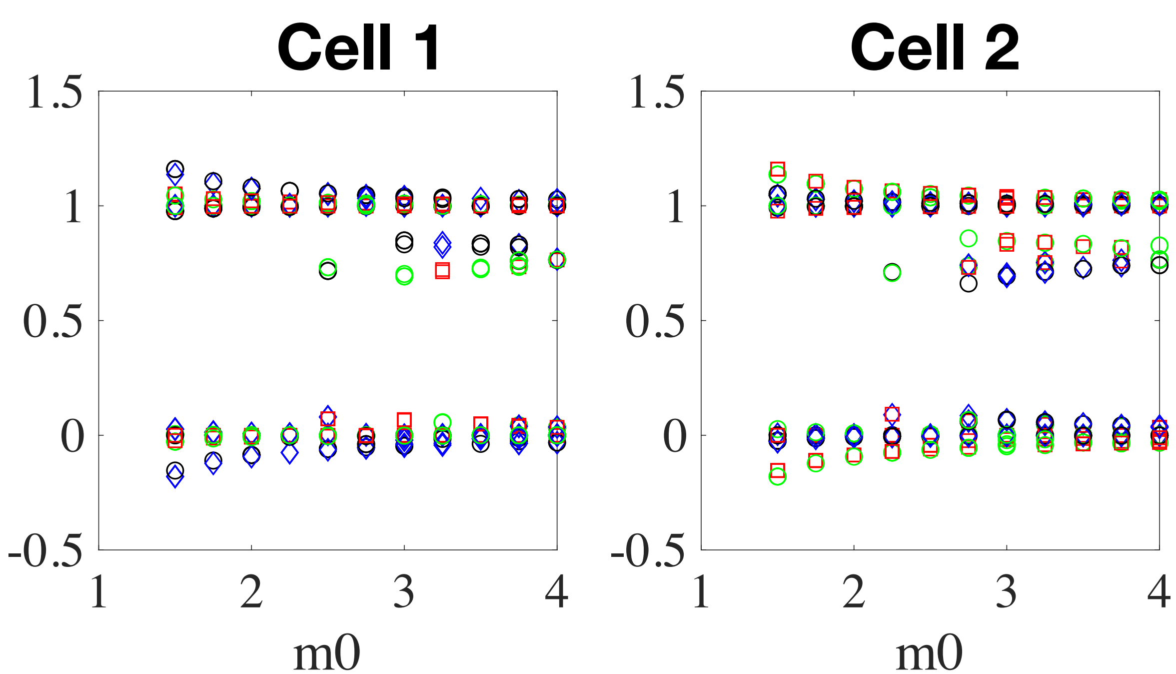
Emergent distributions of actin networks in both cells



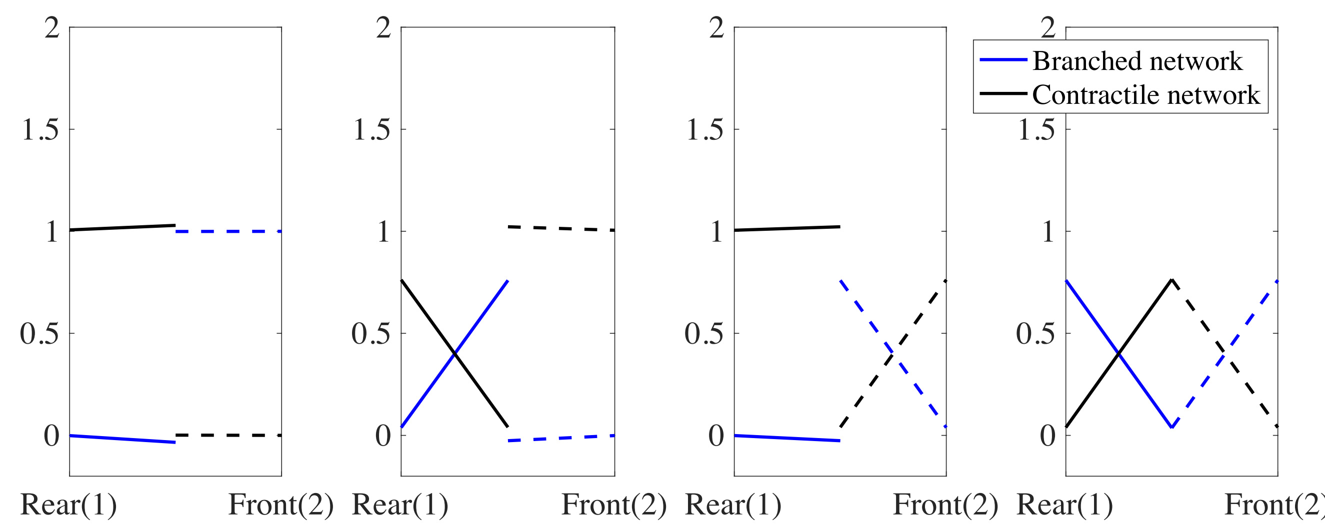
Self-inhibition
cell-cell coupling



D = 0.1, α = -0.1, β = 0, γ = -0.1, δ = 0

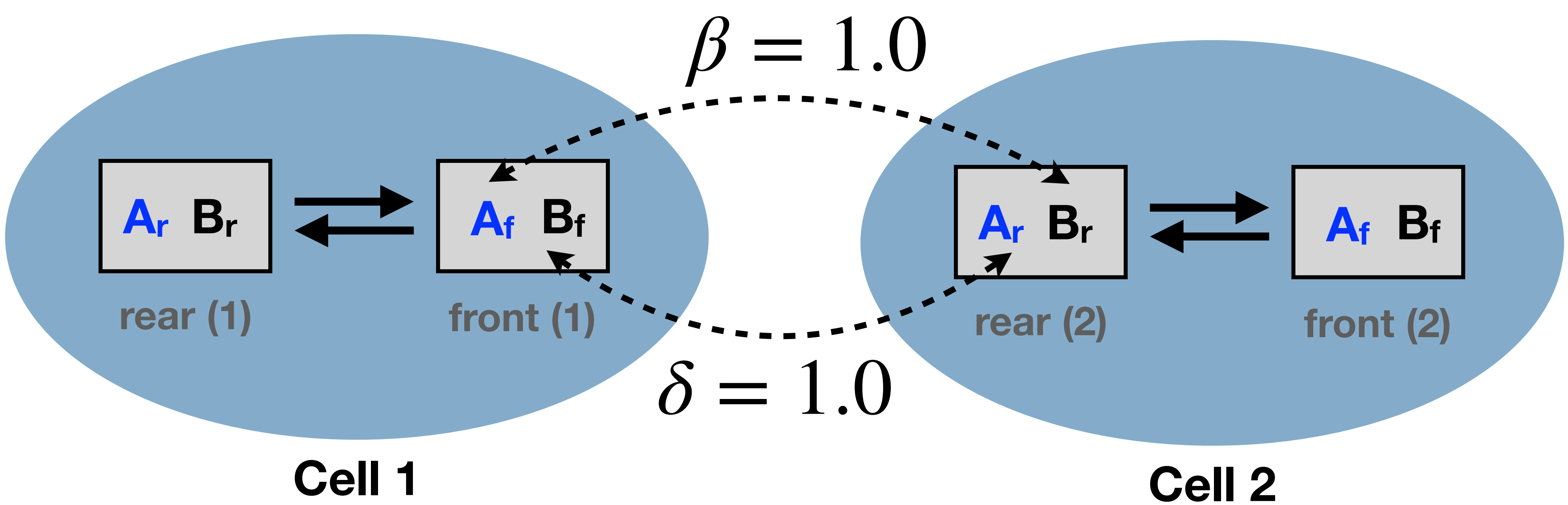


Emergent distributions of actin networks in both cells

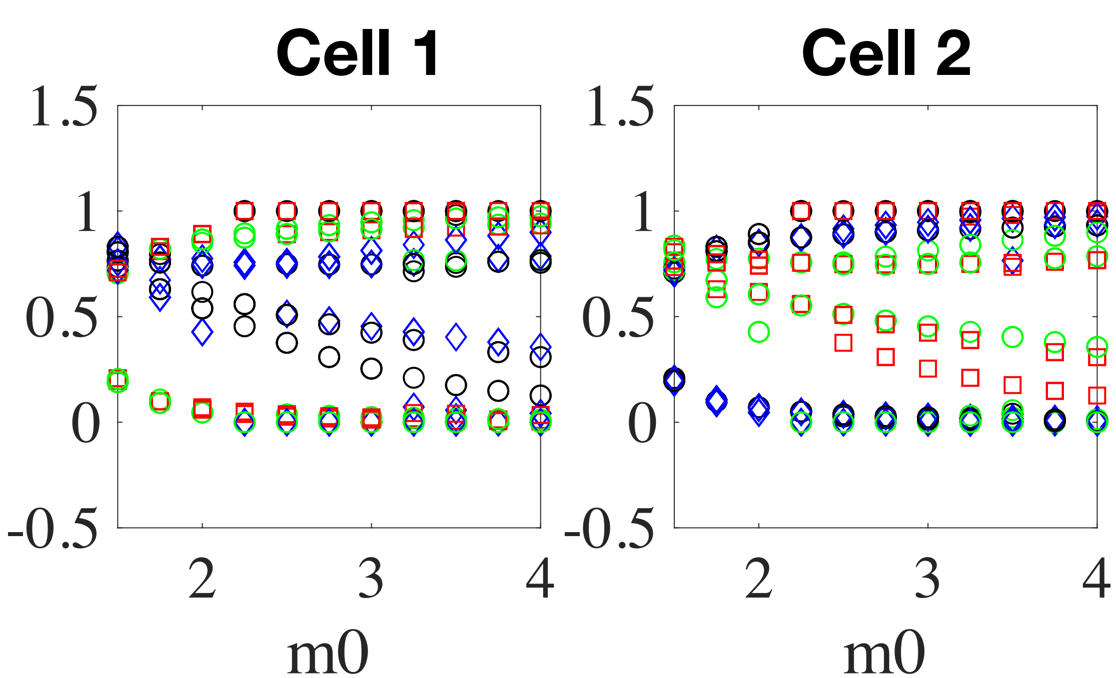


Polarized solutions emerge for larger competition constant.
Perturbations of no coupling scenario

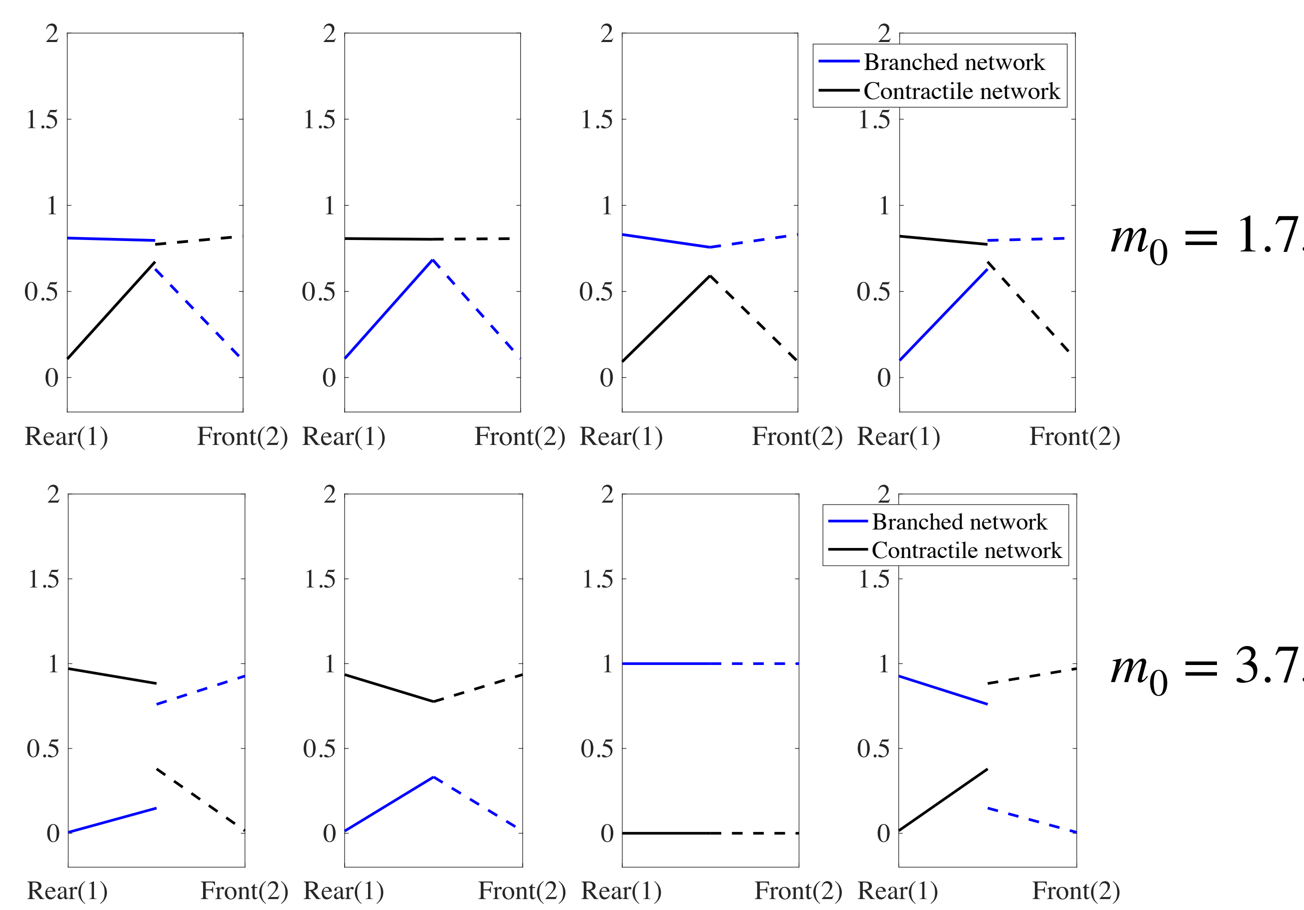
Contact promotion cell-cell coupling



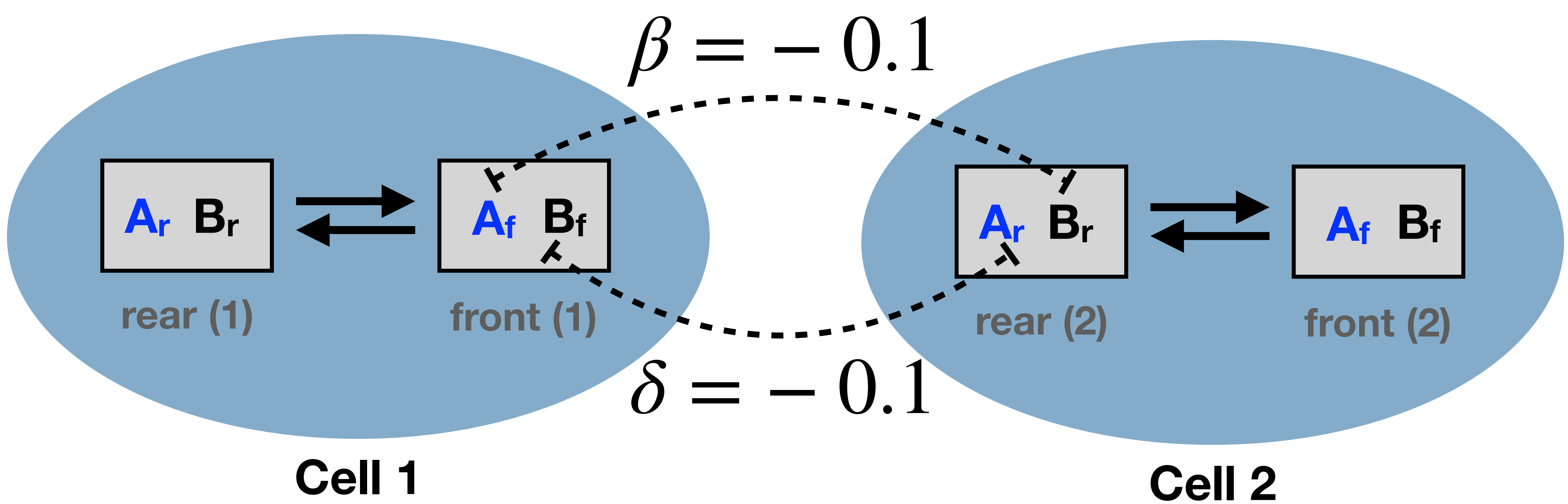
D = 0.1, α = 0, β = 1, γ = 0, δ = 1



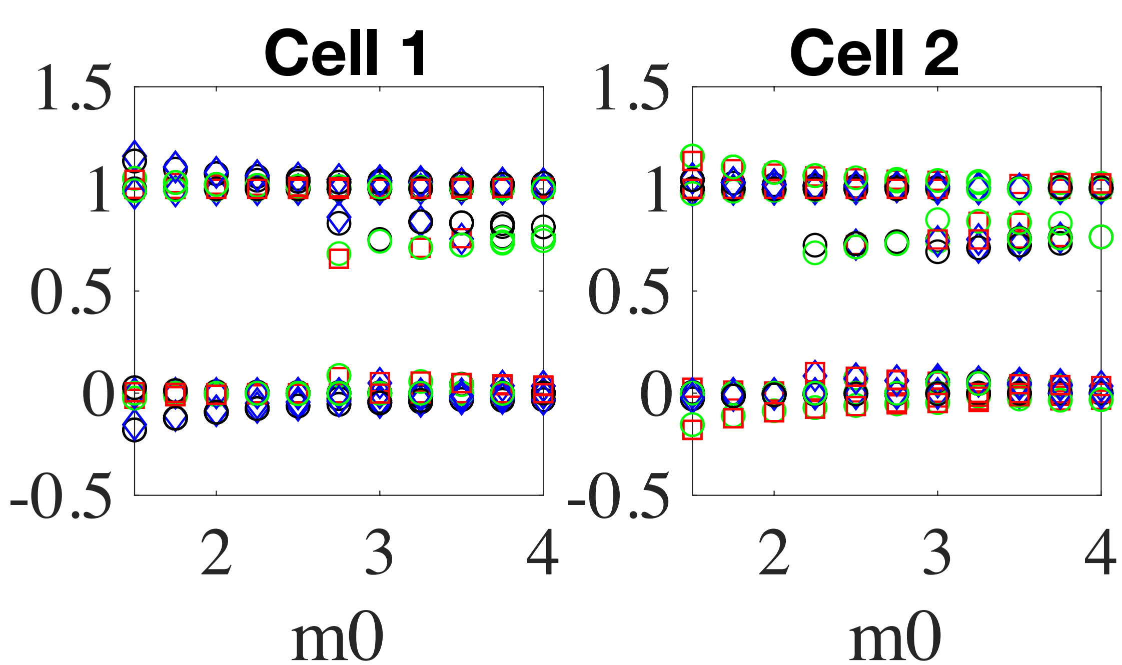
Emergent distributions of actin networks in both cells



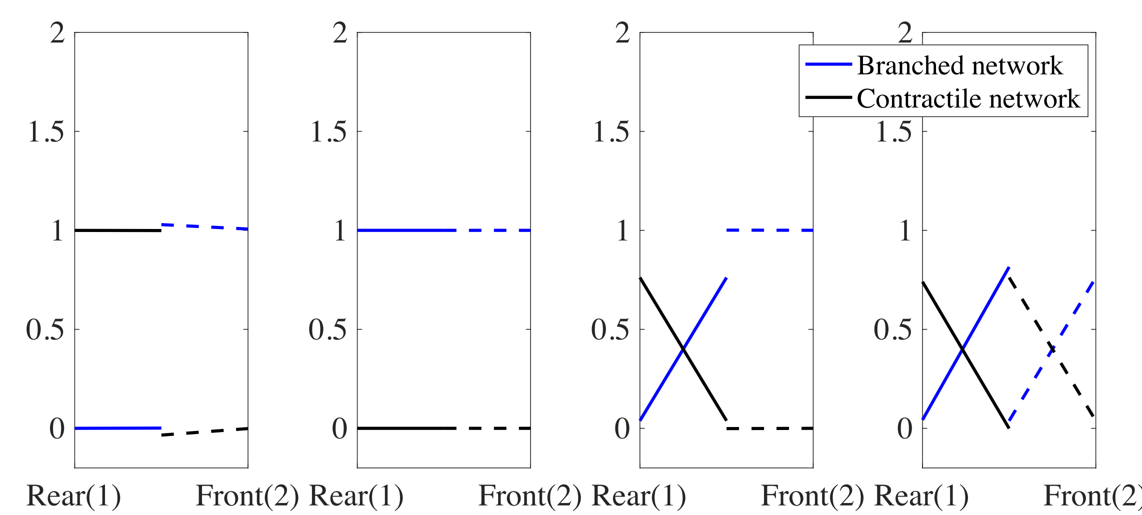
Contact inhibition
cell-cell coupling



D = 0.1, α = 0, β = -0.1, γ = 0, δ = -0.1

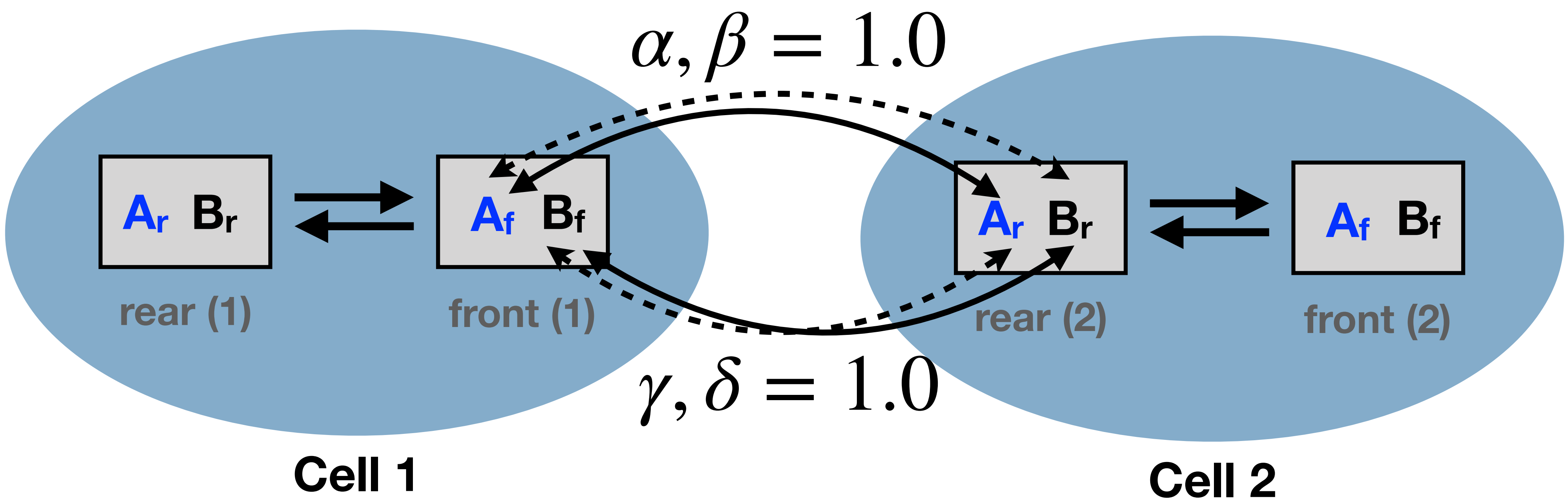


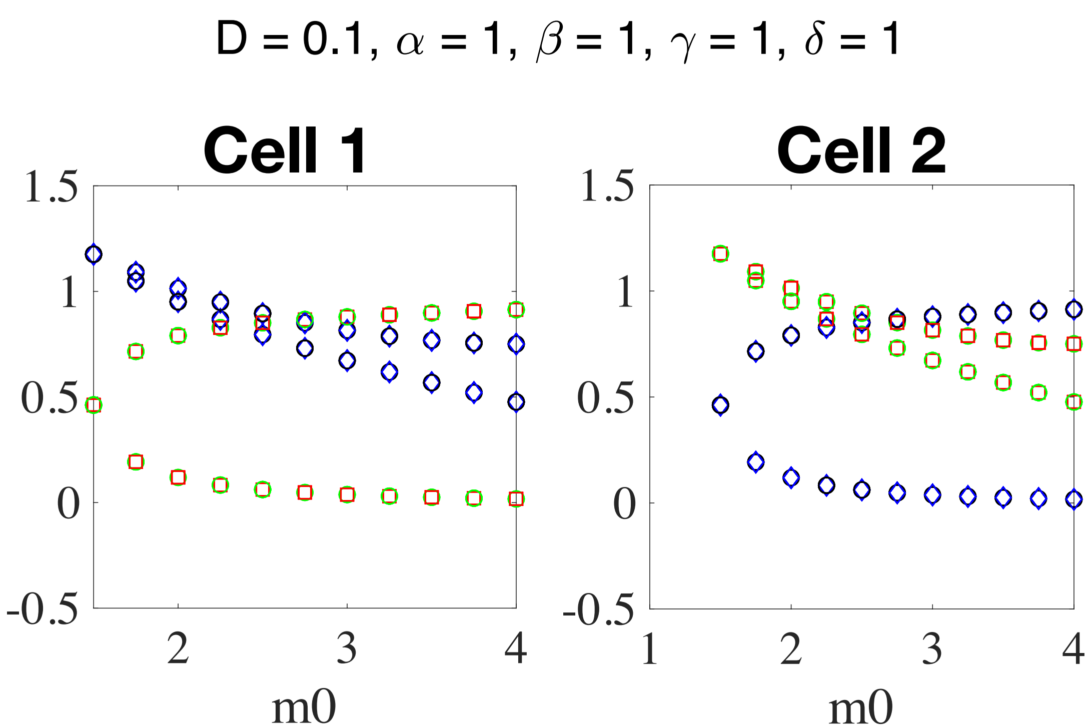
Emergent distributions of actin networks in both cells



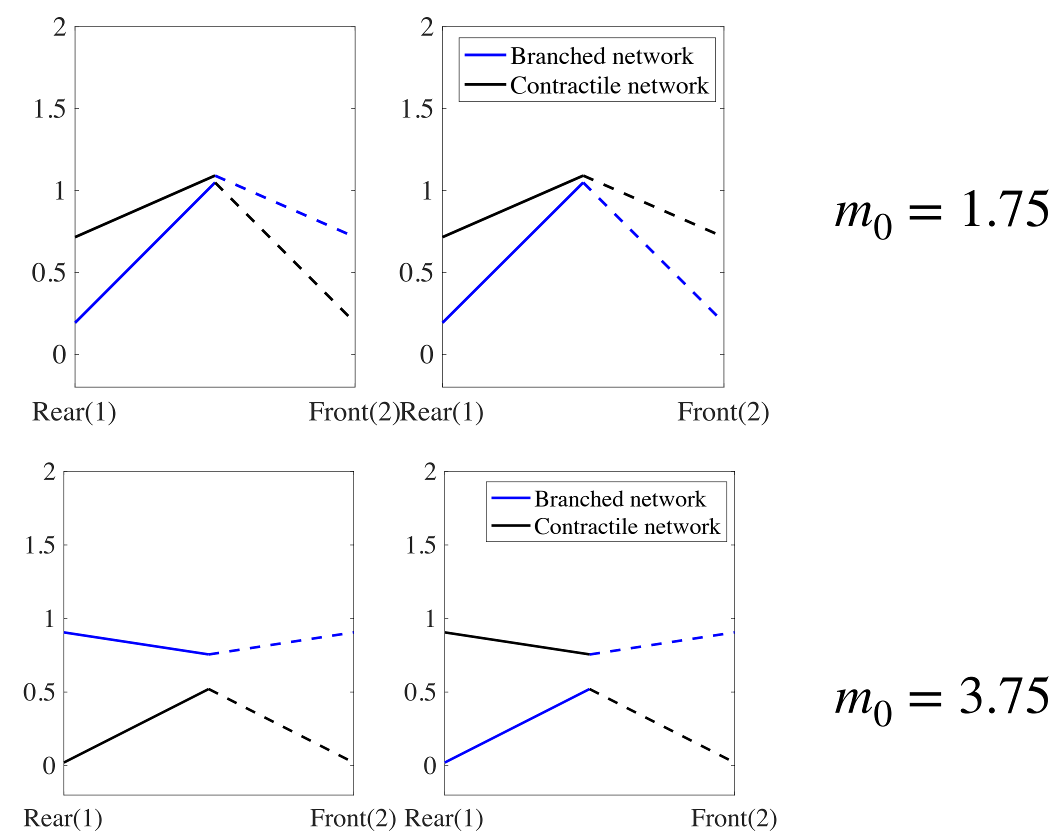
Polarized solutions emerge for larger competition constant.
Perturbations of no coupling scenario

Cross promotion cell-cell coupling

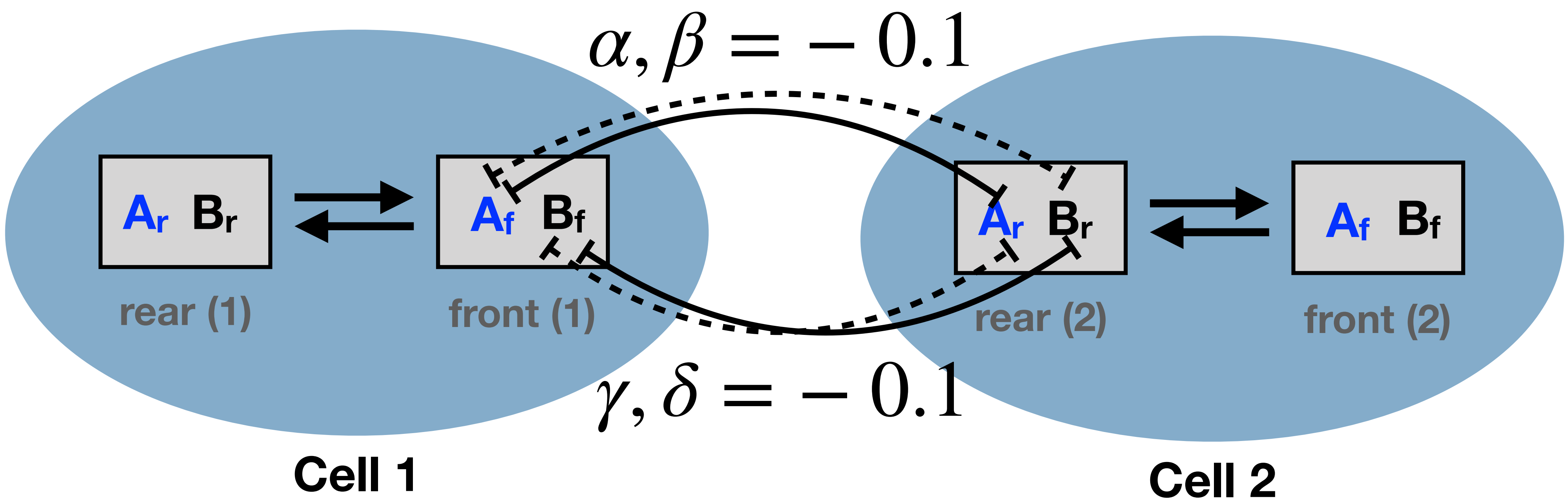




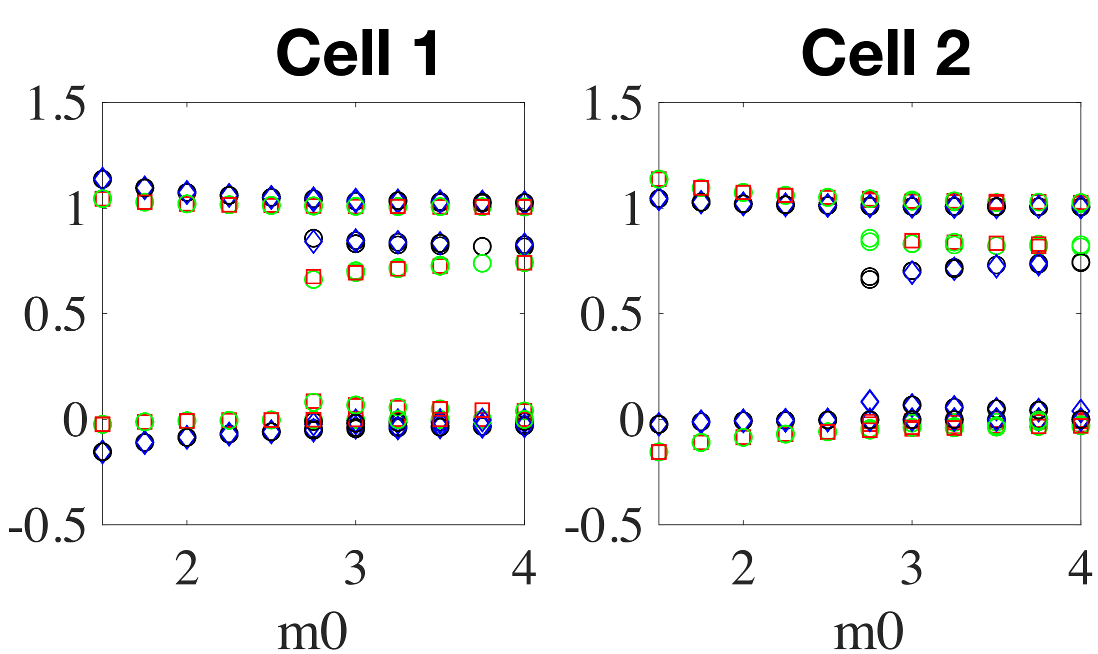
Emergent distributions of actin networks in both cells



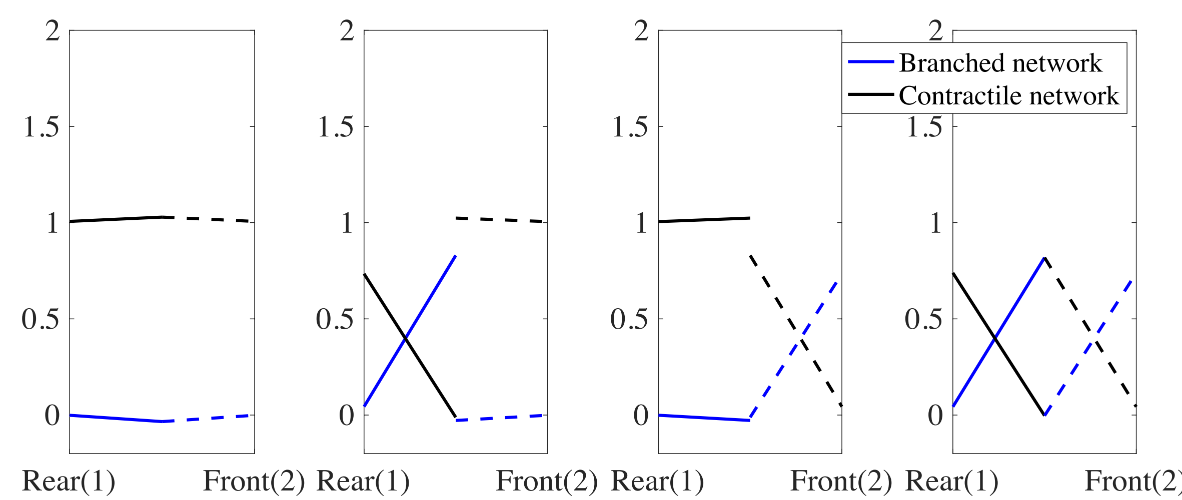
Cross inhibition cell-cell coupling



D = 0.1, α = -0.1, β = -0.1, γ = -0.1, δ = -0.1

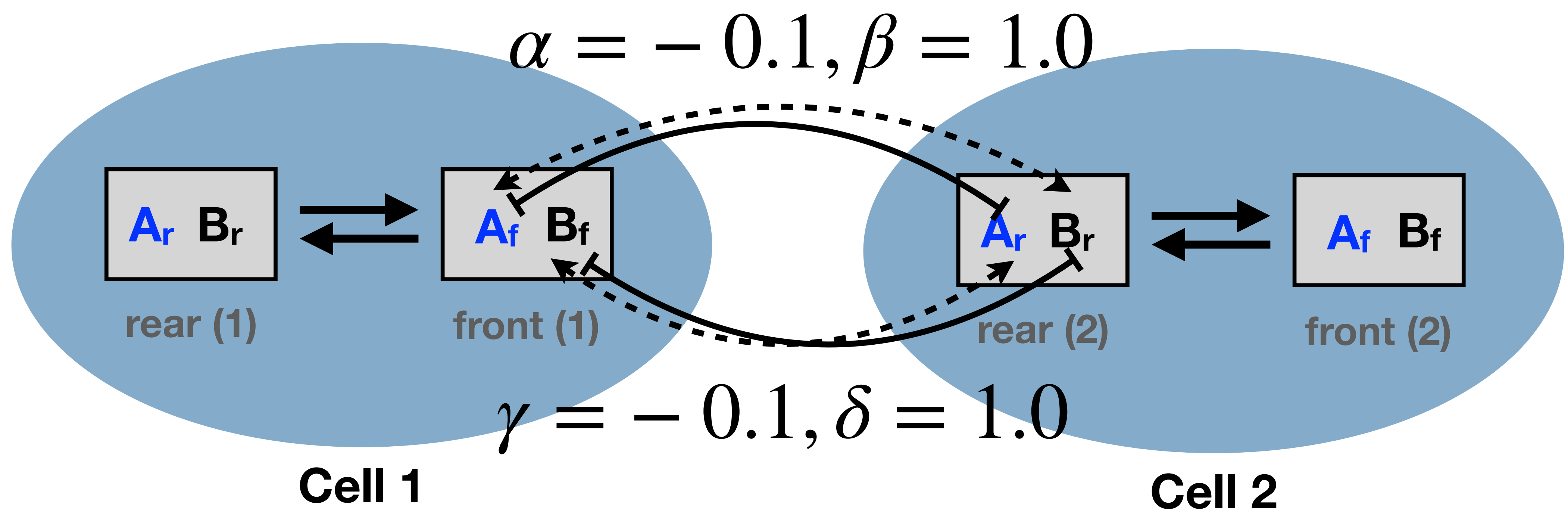


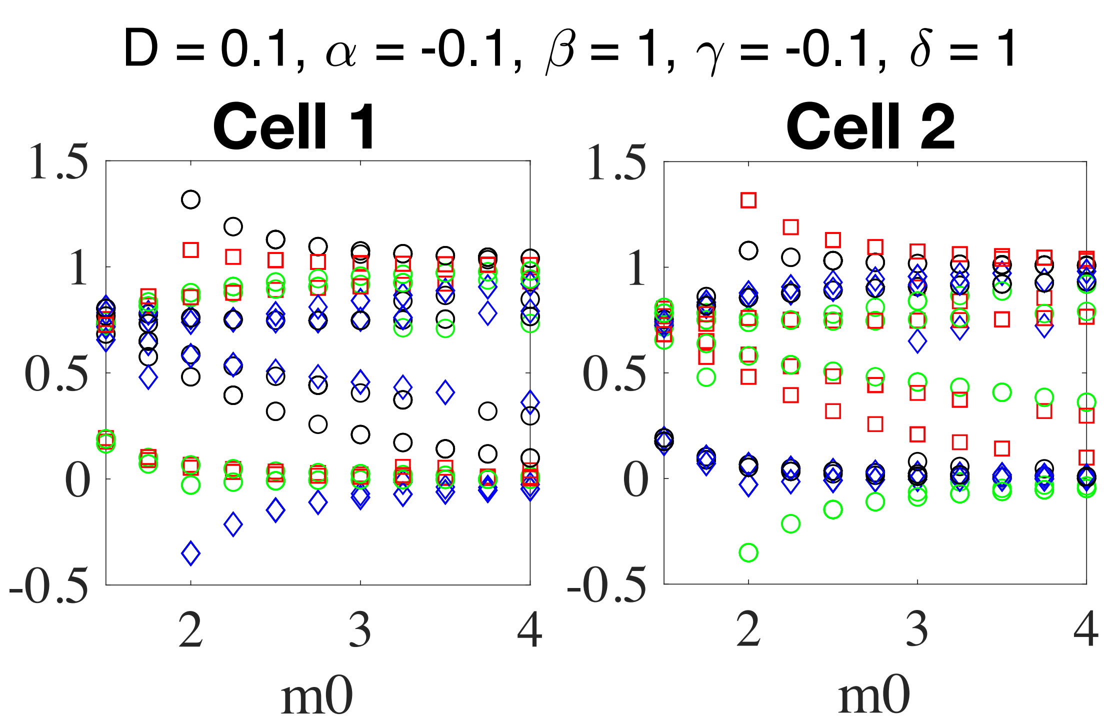
Emergent distributions of actin networks in both cells



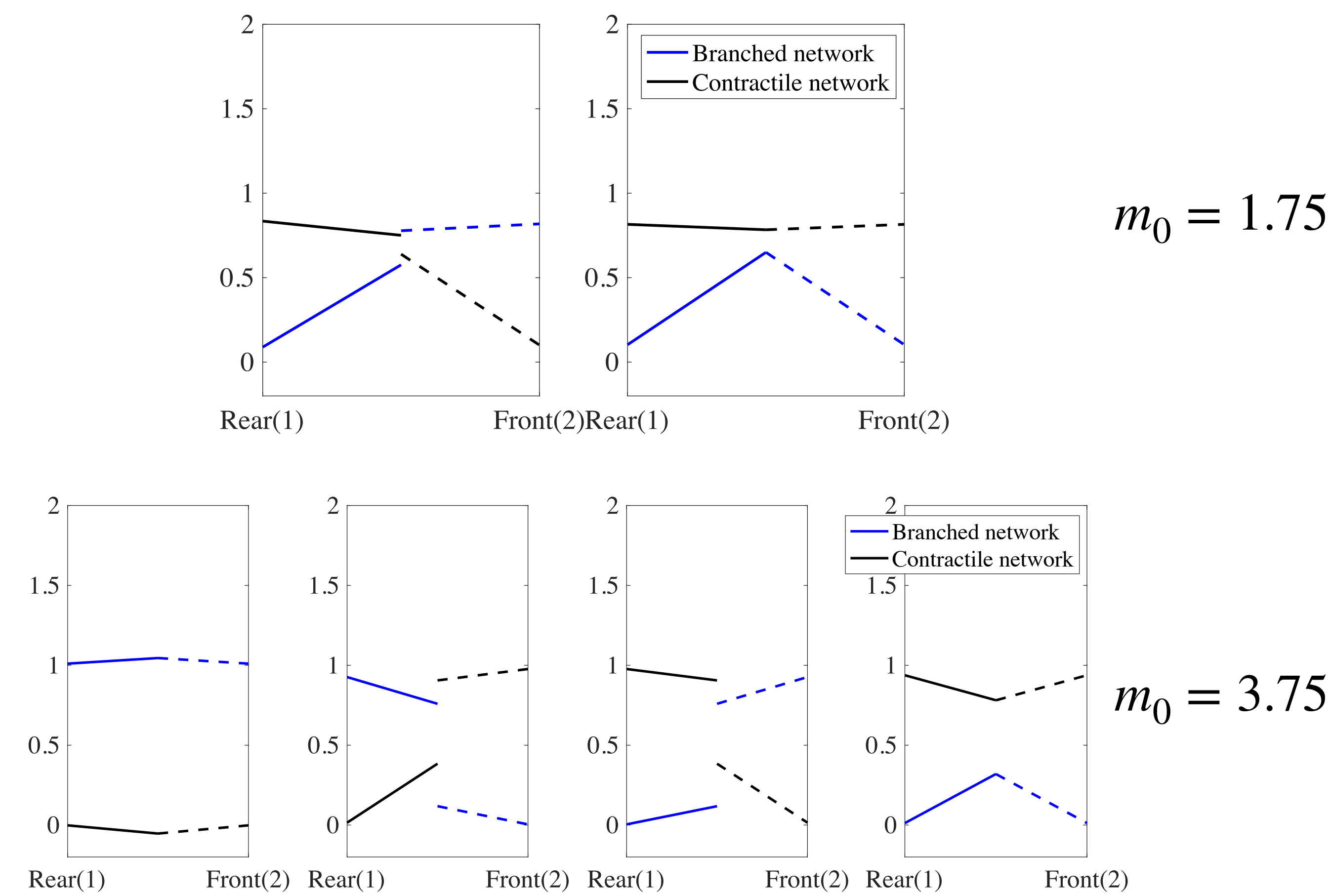
Polarized solutions emerge for larger competition constant.
Perturbations of no coupling scenario

Contact promotion & self-inhibition cell-cell coupling

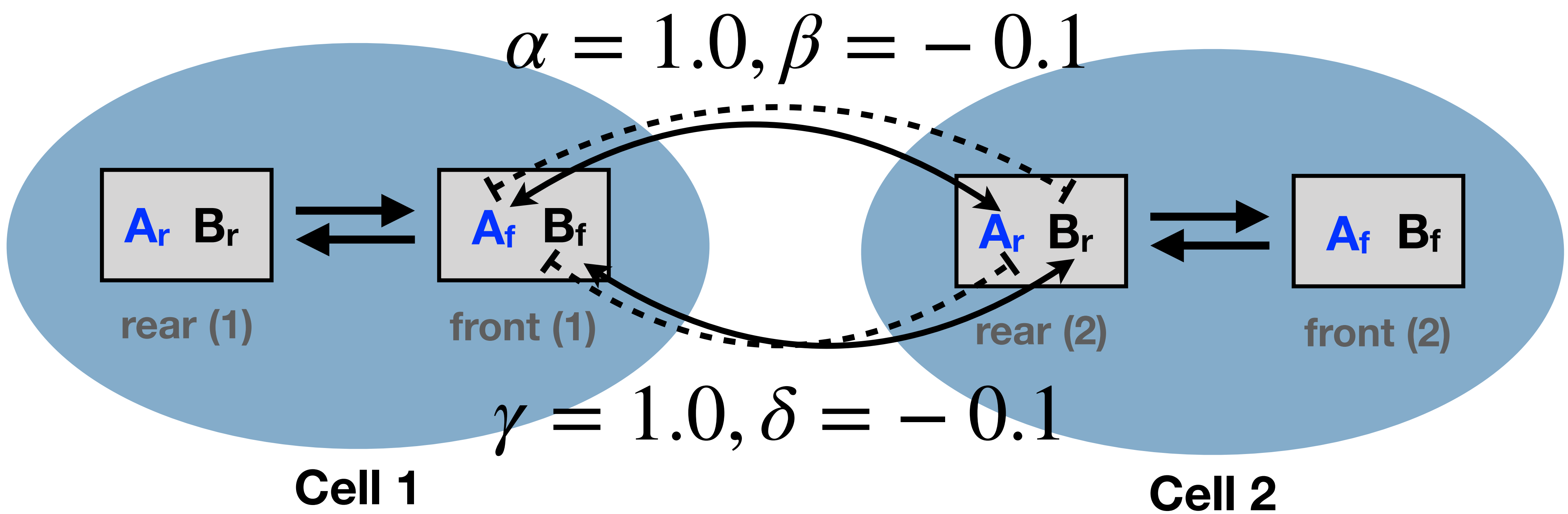




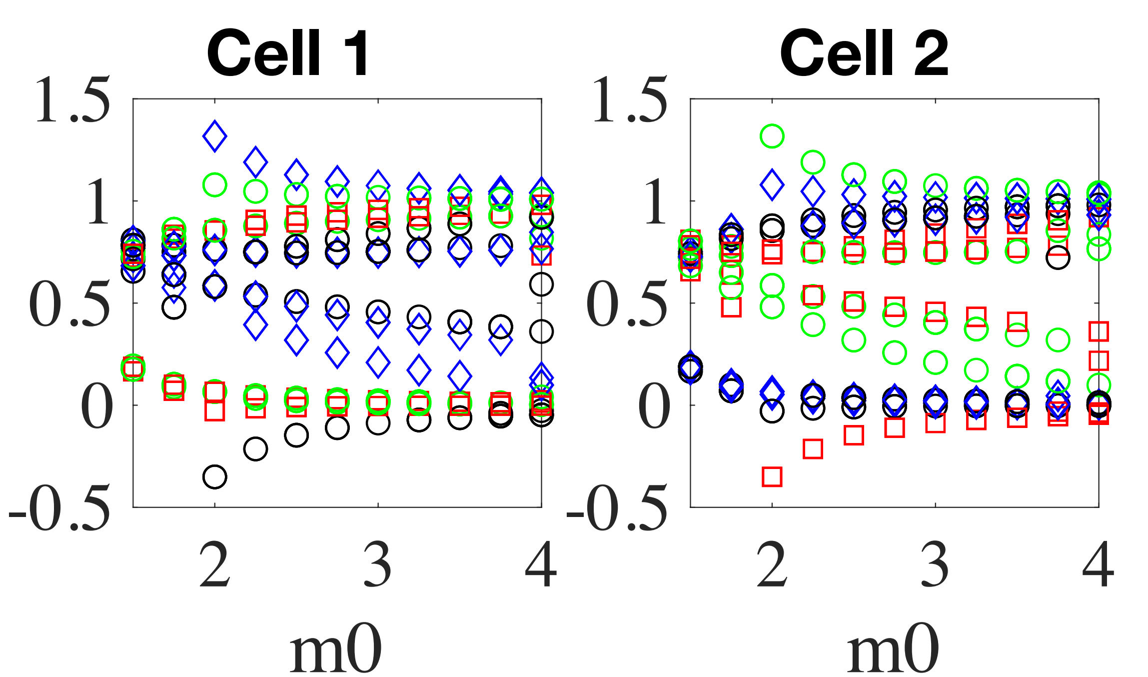
Emergent distributions of actin networks in both cells



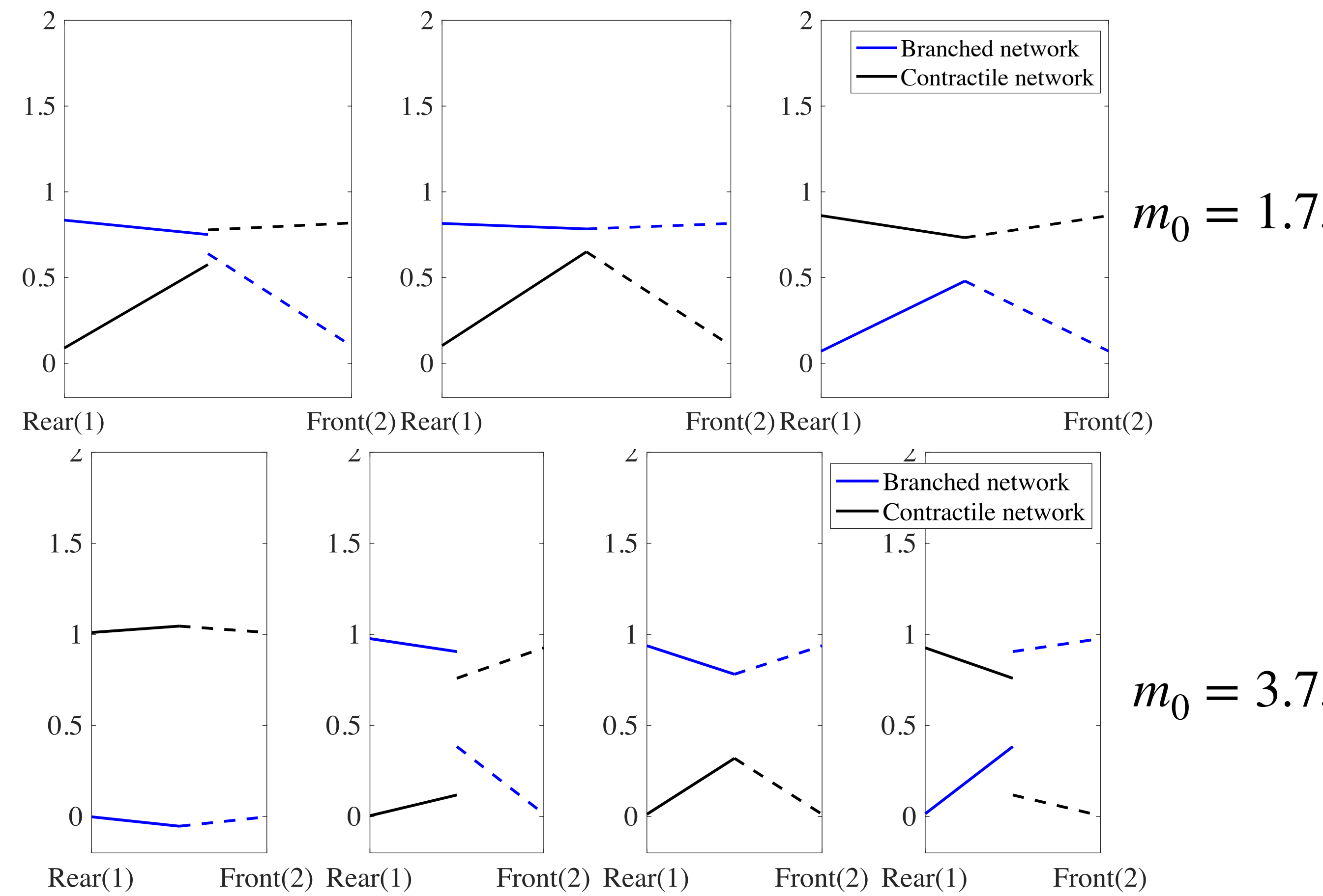
Contact inhibition & self-promotion cell-cell coupling

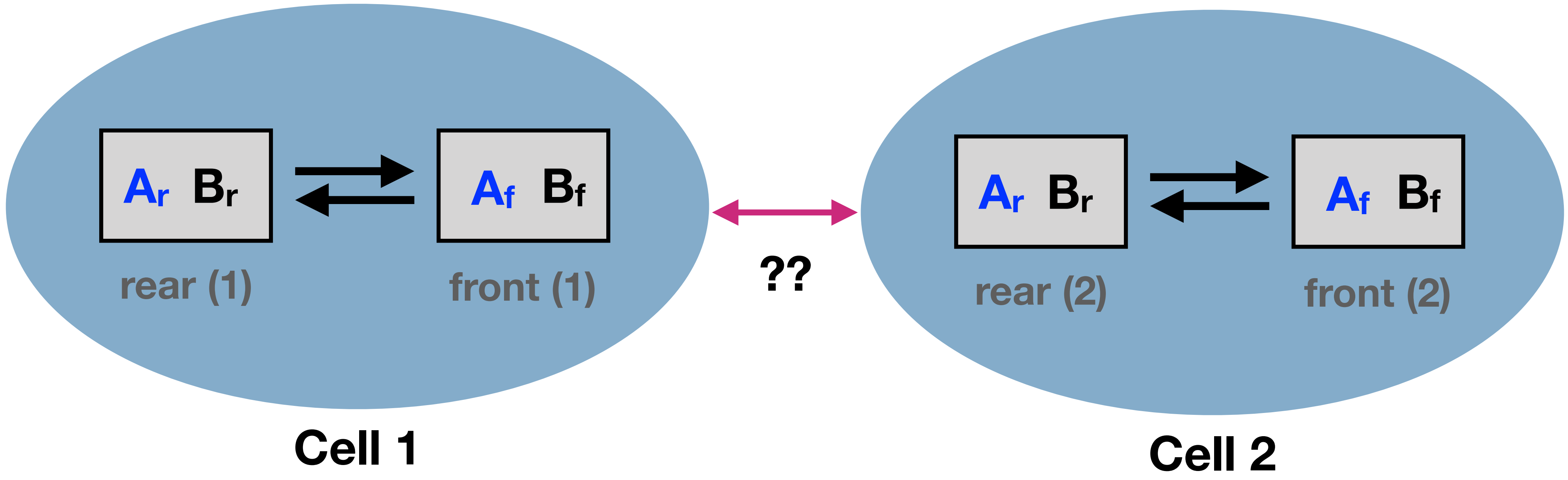


D = 0.1, α = 1, β = -0.1, γ = 1, δ = -0.1



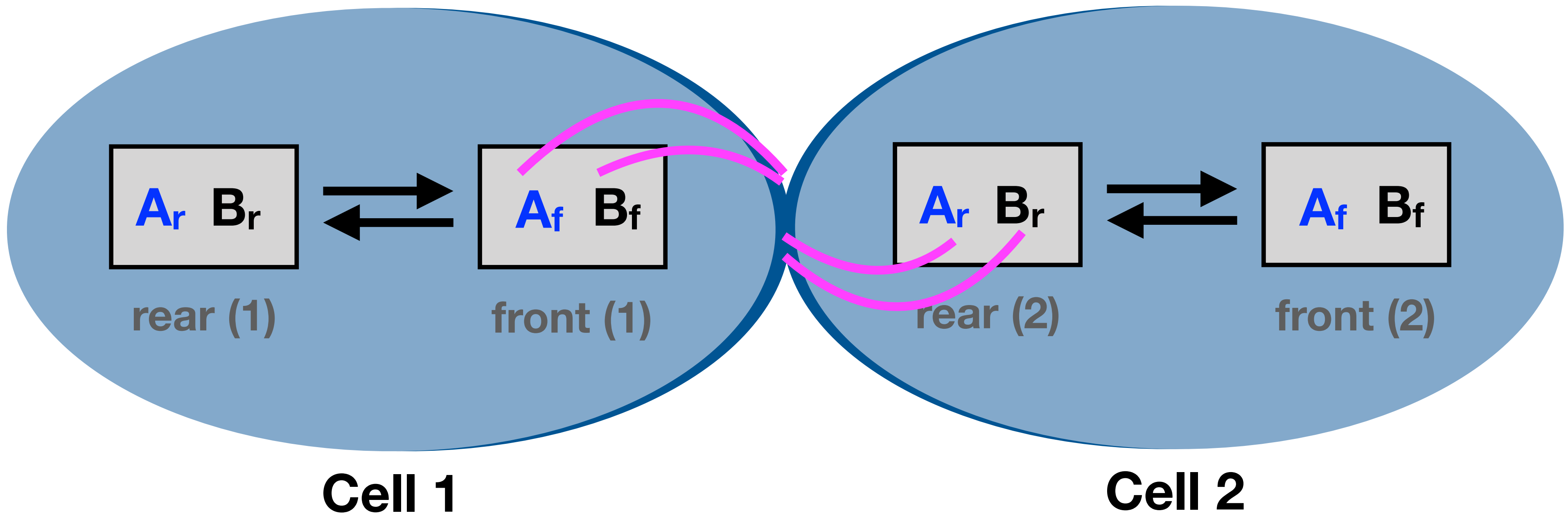
Emergent distributions of actin networks in both cells





Summary of results on cell-cell coupling models:

- ~~No coupling~~
- Self-promotion
- ~~Self-inhibition~~
- Contact promotion
- ~~Contact inhibition~~
- Cross promotion
- ~~Cross inhibition~~
- Contact promotion & self-inhibition
- Contact inhibition & self-promotion



Cell-cell coupling schemes (version 02): boundary regulates actin

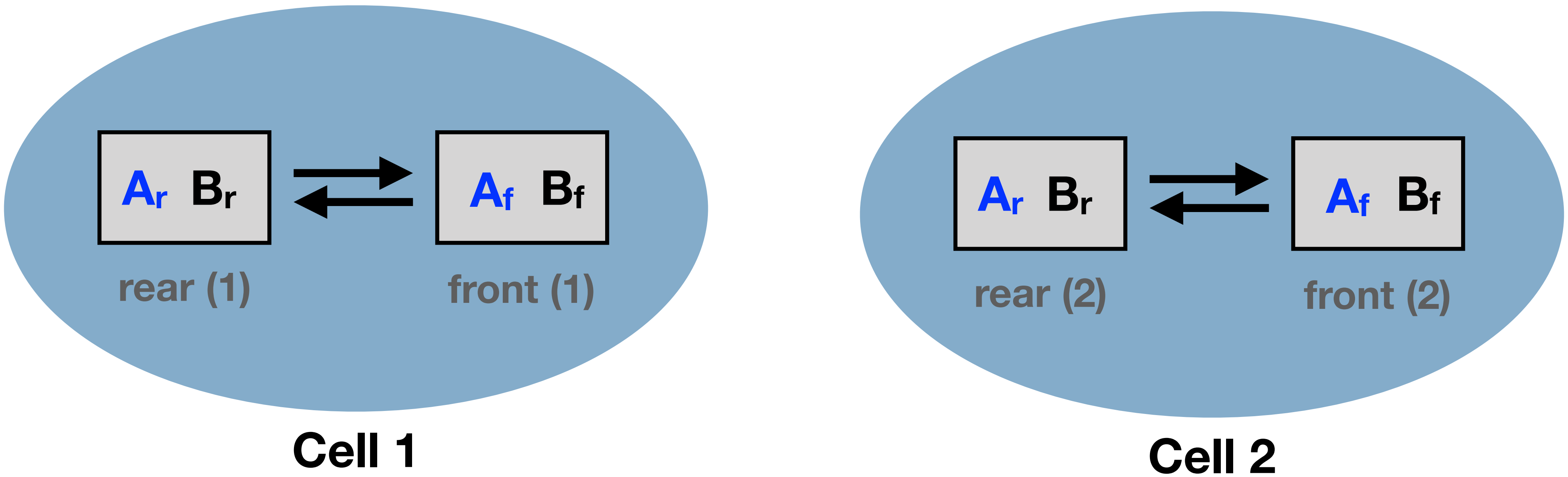
Cell 1

$$\begin{cases} \frac{dA_{1,f}}{dt} = \boxed{(1+\alpha)} A_{1,f} - A_{1,f}^2 - m_0 A_{1,f} B_{1,f} + D(A_{1,r} - A_{1,f}) \\ \frac{dB_{1,f}}{dt} = \boxed{(1+\gamma)} B_{1,f} - B_{1,f}^2 - m_0 A_{1,f} B_{1,f} + D(B_{1,r} - B_{1,f}) \\ \frac{dA_{1,r}}{dt} = A_{1,r} - A_{1,r}^2 - m_0 A_{1,r} B_{1,r} + D(A_{1,f} - A_{1,r}) \\ \frac{dB_{1,r}}{dt} = B_{1,r} - B_{1,r}^2 - m_0 A_{1,r} B_{1,r} + D(B_{1,f} - B_{1,r}) \end{cases}$$

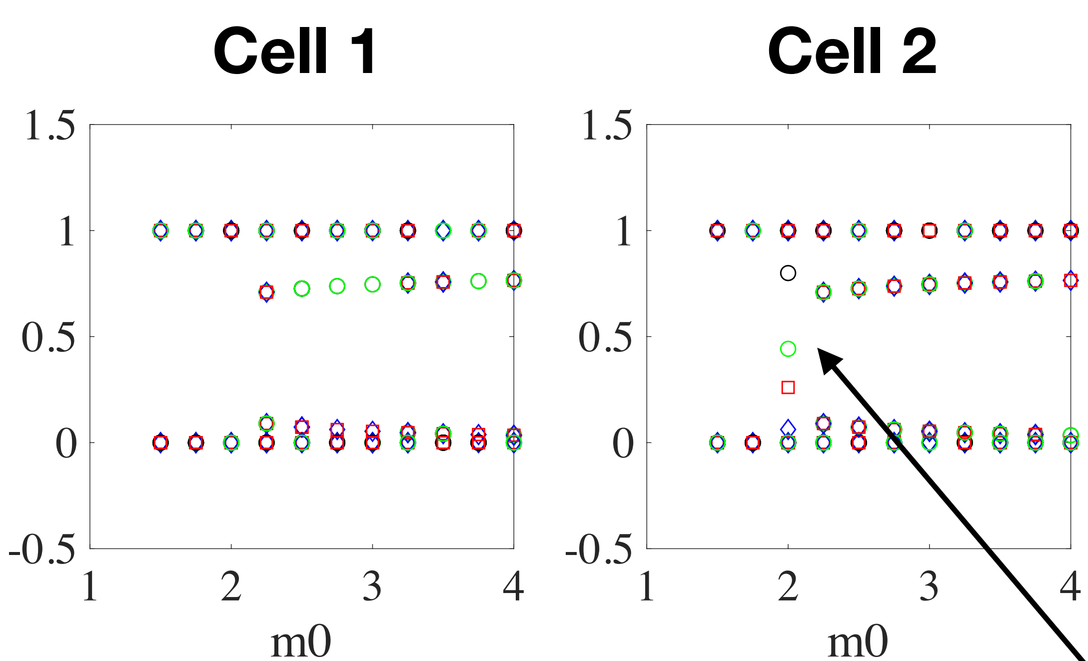
Cell 2

$$\begin{cases} \frac{dA_{2,f}}{dt} = A_{2,f} - A_{2,f}^2 - m_0 A_{2,f} B_{2,f} + D(A_{2,r} - A_{2,f}) \\ \frac{dB_{2,f}}{dt} = B_{2,f} - B_{2,f}^2 - m_0 A_{2,f} B_{2,f} + D(B_{2,r} - B_{2,f}) \\ \frac{dA_{2,r}}{dt} = \boxed{(1+\beta)} A_{2,r} - A_{2,r}^2 - m_0 A_{2,r} B_{2,r} + D(A_{2,f} - A_{2,r}) \\ \frac{dB_{2,r}}{dt} = \boxed{(1+\delta)} B_{2,r} - B_{2,r}^2 - m_0 A_{2,r} B_{2,r} + D(B_{2,f} - B_{2,r}) \end{cases}$$

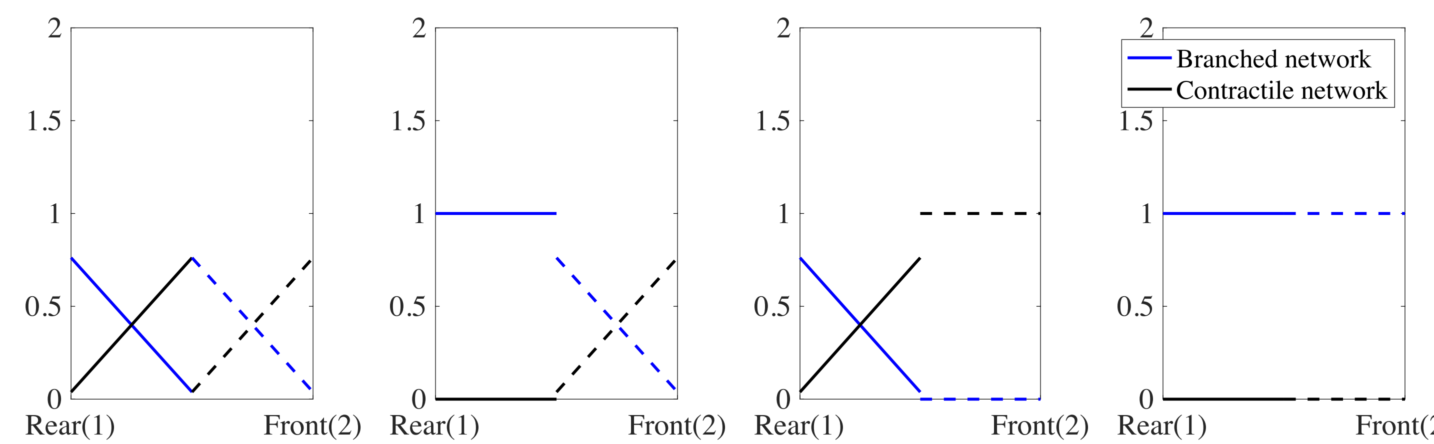
No
cell-cell coupling



D = 0.1, $\alpha = 0$, $\beta = 0$, $\gamma = 0$, $\delta = 0$



Emergent distributions of actin networks in both cells

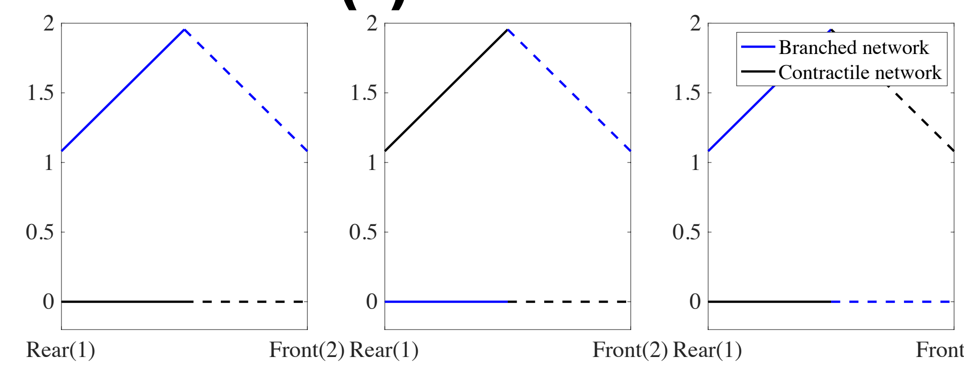


Polarization in each individual cell can happen for m0 > 2

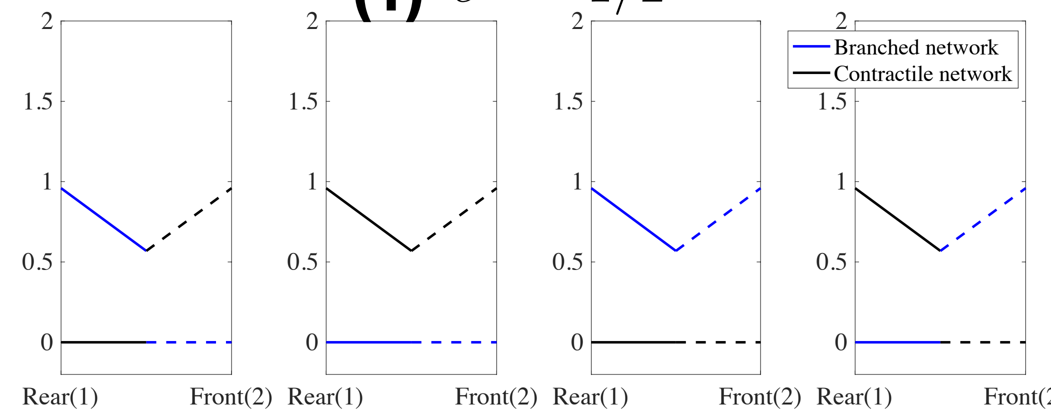
$$
\text{(1)} \begin{cases}
\frac{dA_{1,f}}{dt} = \boxed{(1+\alpha)} A_{1,f} - A_{1,f}^2 - m_0 A_{1,f} B_{1,f} + D(A_{1,r} - A_{1,f}) \\
\frac{dB_{1,f}}{dt} = \boxed{(1+\gamma)} B_{1,f} - B_{1,f}^2 - m_0 A_{1,f} B_{1,f} + D(B_{1,r} - B_{1,f}) \\
\frac{dA_{1,r}}{dt} = A_{1,r} - A_{1,r}^2 - m_0 A_{1,r} B_{1,r} + D(A_{1,f} - A_{1,r}) \\
\frac{dB_{1,r}}{dt} = B_{1,r} - B_{1,r}^2 - m_0 A_{1,r} B_{1,r} + D(B_{1,f} - B_{1,r})
\end{cases}
$$

$$
\text{(2)} \begin{cases}
\frac{dA_{2,f}}{dt} = A_{2,f} - A_{2,f}^2 - m_0 A_{2,f} B_{2,f} + D(A_{2,r} - A_{2,f}) \\
\frac{dB_{2,f}}{dt} = B_{2,f} - B_{2,f}^2 - m_0 A_{2,f} B_{2,f} + D(B_{2,r} - B_{2,f}) \\
\frac{dA_{2,r}}{dt} = \boxed{(1+\beta)} A_{2,r} - A_{2,r}^2 - m_0 A_{2,r} B_{2,r} + D(A_{2,f} - A_{2,r}) \\
\frac{dB_{2,r}}{dt} = \boxed{(1+\delta)} B_{2,r} - B_{2,r}^2 - m_0 A_{2,r} B_{2,r} + D(B_{2,f} - B_{2,r})
\end{cases}
$$

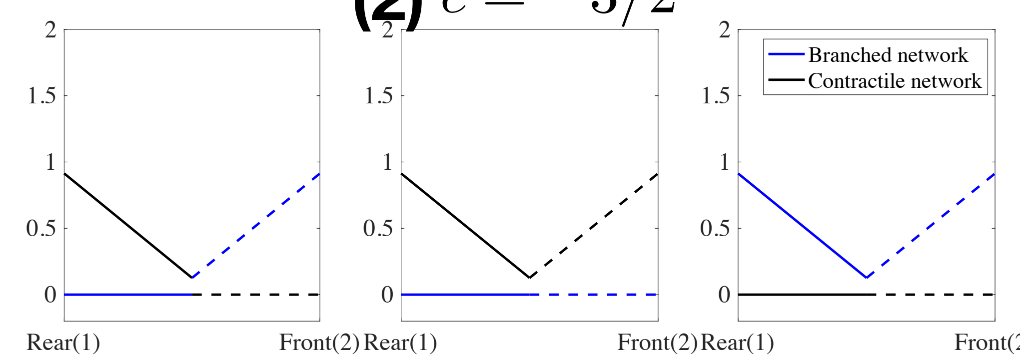
(1) $c = 2$



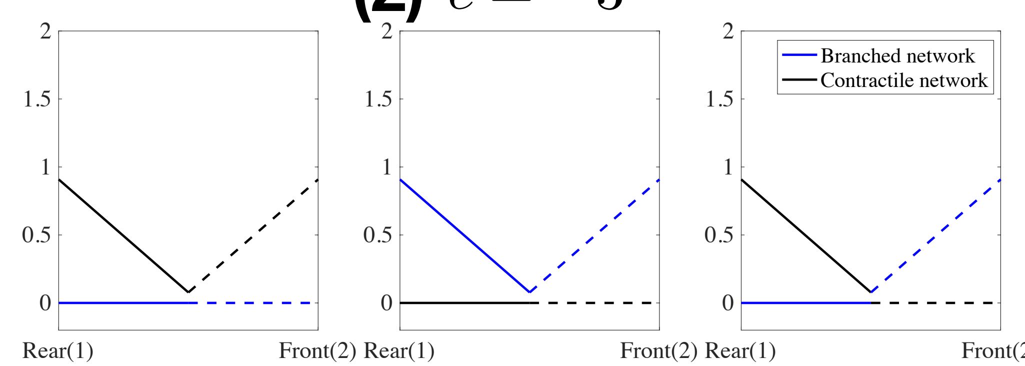
(1) $c = -1/2$



(2) $c = -3/2$



(2) $c = -3$



<u>'Failed' cases:</u>

(1) Self-promotion: $\alpha, \beta, \gamma, \delta = c$

- (c = 2, -1/2) **winner takes all with gradients**

(2) Self-inhibition:

- (c = -3/2, -3) **winner takes all with gradients**

(3) Promote branched actin in both cells:

$$\alpha = \beta = 1, \gamma = \delta = 0$$

- **winner takes all with gradients**

(4) Promote bundled actin in both cells:

$$\alpha = \beta = 0, \gamma = \delta = 1$$

- **winner takes all with gradients**

(5) Promote branched actin in cell 1, promote bundled actin in cell 2:

$$\alpha = 1, \beta = 0, \gamma = 0, \delta = 1$$

- **winner takes all with gradients**

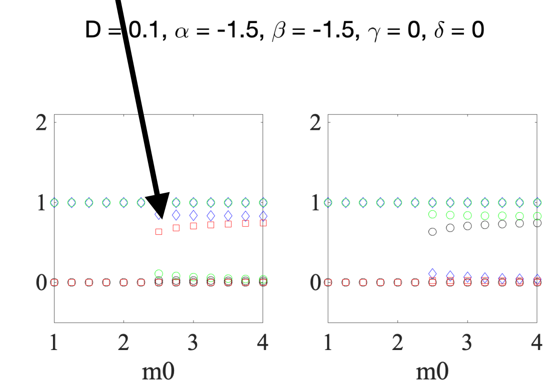
$$(1)\begin{cases}\frac{dA_{1,f}}{dt} = \boxed{(1+\alpha)}A_{1,f} - A_{1,f}^2 - m_0 A_{1,f}B_{1,f} + D(A_{1,r} - A_{1,f})\\ \frac{dB_{1,f}}{dt} = \boxed{(1+\gamma)}B_{1,f} - B_{1,f}^2 - m_0 A_{1,f}B_{1,f} + D(B_{1,r} - B_{1,f})\\ \frac{dA_{1,r}}{dt} = A_{1,r} - A_{1,r}^2 - m_0 A_{1,r}B_{1,r} + D(A_{1,f} - A_{1,r})\\ \frac{dB_{1,r}}{dt} = B_{1,r} - B_{1,r}^2 - m_0 A_{1,r}B_{1,r} + D(B_{1,f} - B_{1,r})\end{cases}$$

$$(2)\begin{cases}\frac{dA_{2,f}}{dt} = A_{2,f} - A_{2,f}^2 - m_0 A_{2,f}B_{2,f} + D(A_{2,r} - A_{2,f})\\ \frac{dB_{2,f}}{dt} = B_{2,f} - B_{2,f}^2 - m_0 A_{2,f}B_{2,f} + D(B_{2,r} - B_{2,f})\\ \frac{dA_{2,r}}{dt} = \boxed{(1+\beta)}A_{2,r} - A_{2,r}^2 - m_0 A_{2,r}B_{2,r} + D(A_{2,f} - A_{2,r})\\ \frac{dB_{2,r}}{dt} = \boxed{(1+\delta)}B_{2,r} - B_{2,r}^2 - m_0 A_{2,r}B_{2,r} + D(B_{2,f} - B_{2,r})\end{cases}$$

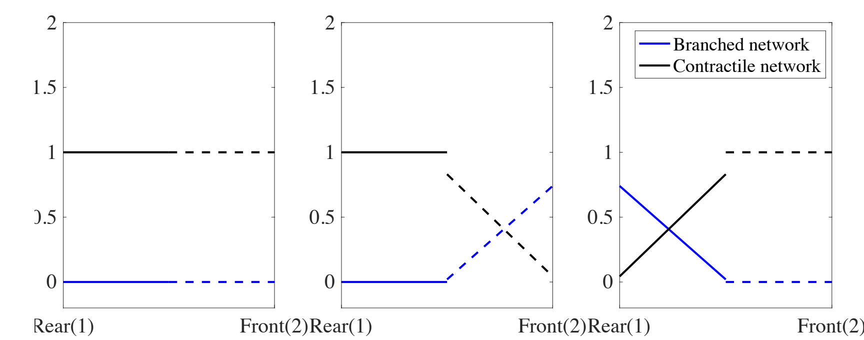
Polarization in each individual cell can happen for m0 > 2.5

‘Successful’ cases:

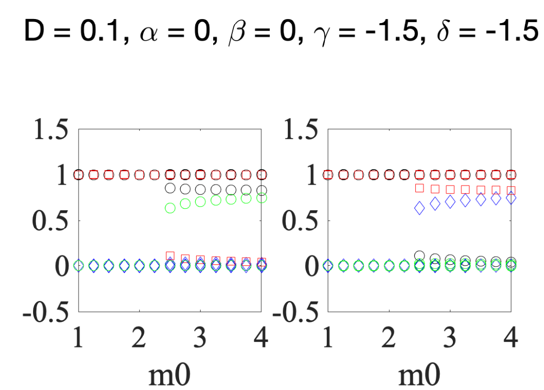
- polarized solution in a cell or both cells exist



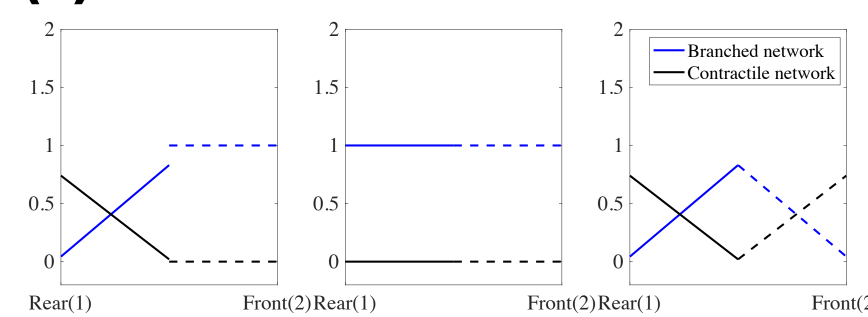
(6)



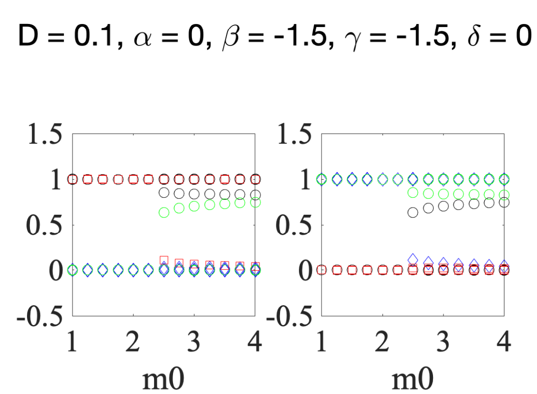
(6) Inhibit branched actin in both cells:
$$\alpha, \beta = -1.5, \gamma, \delta = 0$$



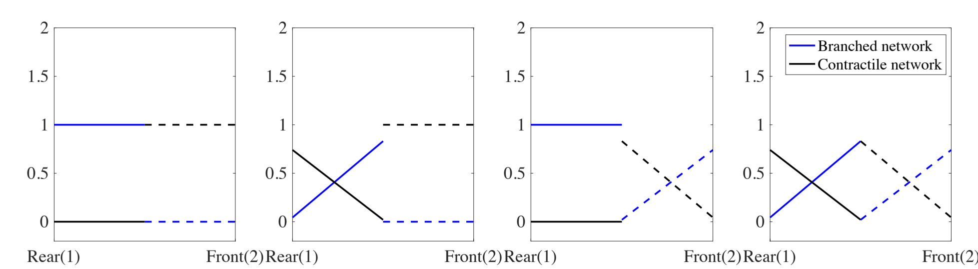
(7)



(7) Inhibit bundled actin in both cells:
$$\alpha, \beta = 0, \gamma, \delta = -1.5$$



(8)



(8) Inhibit bundled actin in cell 1, inhibit branched actin in cell 2:
$$\alpha = 0, \beta = -1.5, \gamma = -1.5, \delta = 0$$

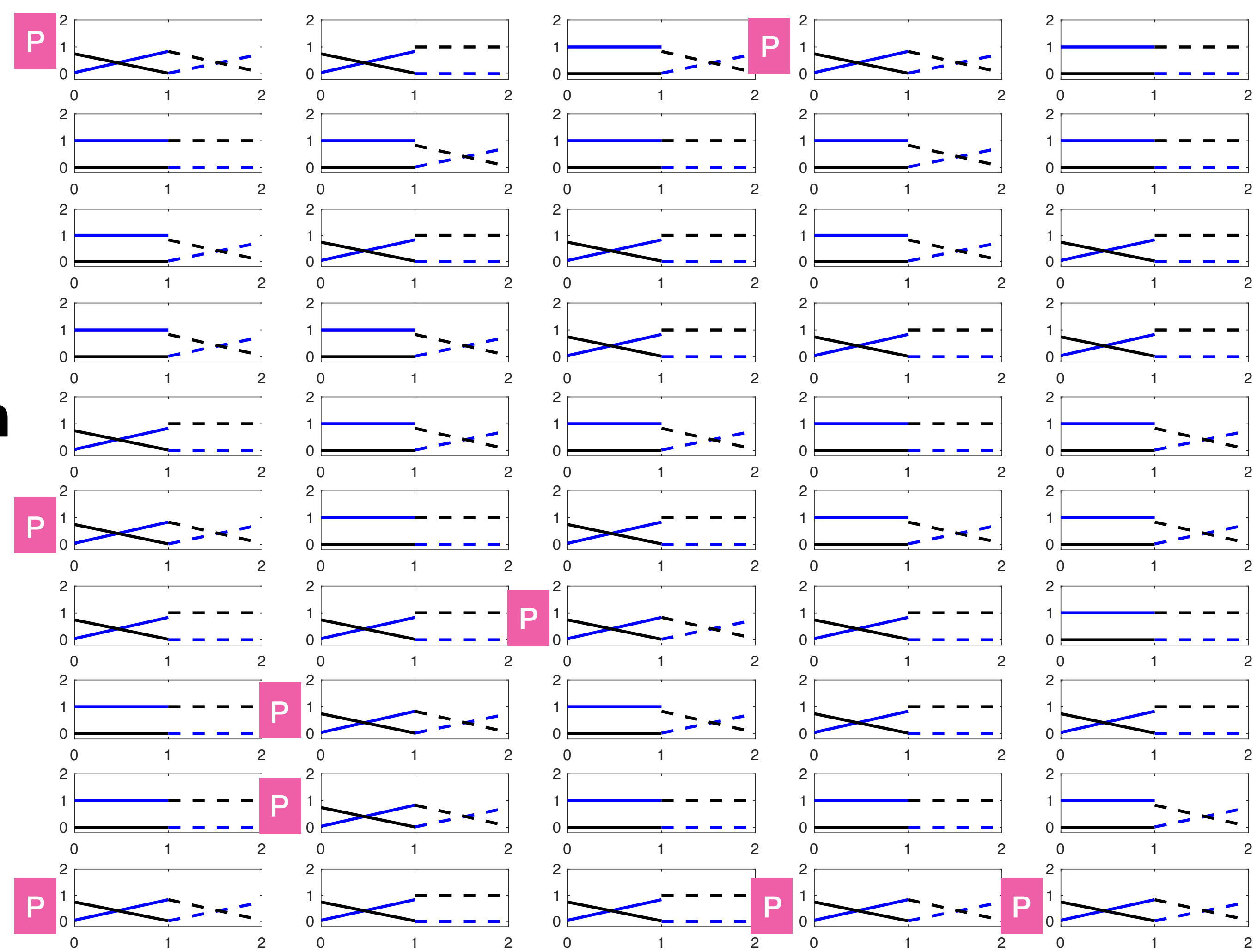
Did polarization ability improve in either of the ‘successful’ models?

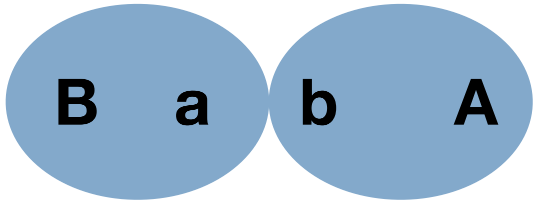
Case	# correctly polarized solutions	Notes
Default (no coupling)	2/50	
06 (inhibit branched in both)	0/50	protrusion at leading edge for both cells
07 (inhibit bundled in both)	0/50	protrusion at cell-cell contact region
08 (inhibit branched/bundled)	12/50	Depends on value for constants (9-12/50)

Case 08: (50 realizations with different initial conditions)

bundled

branched





bundled

branched

Slight modification of case 08:
(50 realizations with different initial conditions)

$D = 0.1,\ \alpha = -0.4,\ \beta = -3,\ \gamma = -3,\ \delta = -0.4$