

Juxtacrine Signaling via First-Neighbor Interactions

Lateral inhibition feedback networks form boundaries and repeating patterns by destabilizing symmetric expression of fate-genes in the embryo:

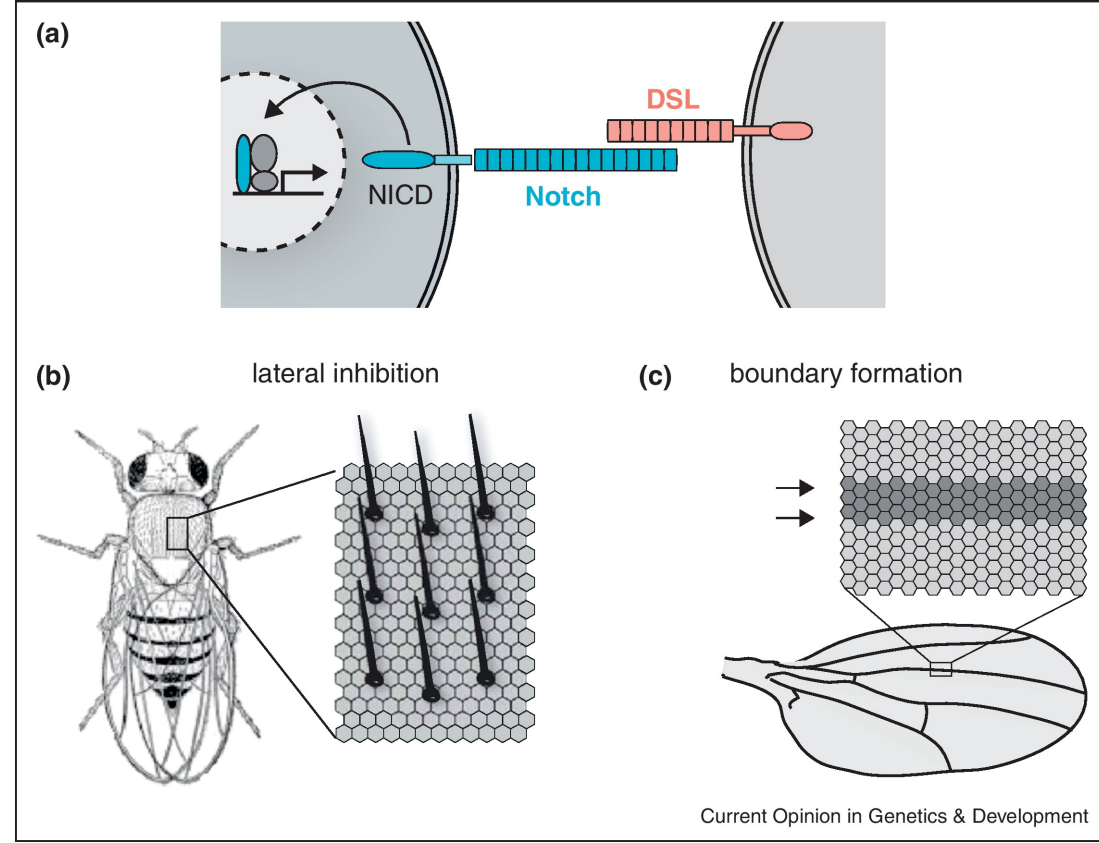


Figure 1. Notch-Delta signaling controls patterning in neuronal lineages [1]

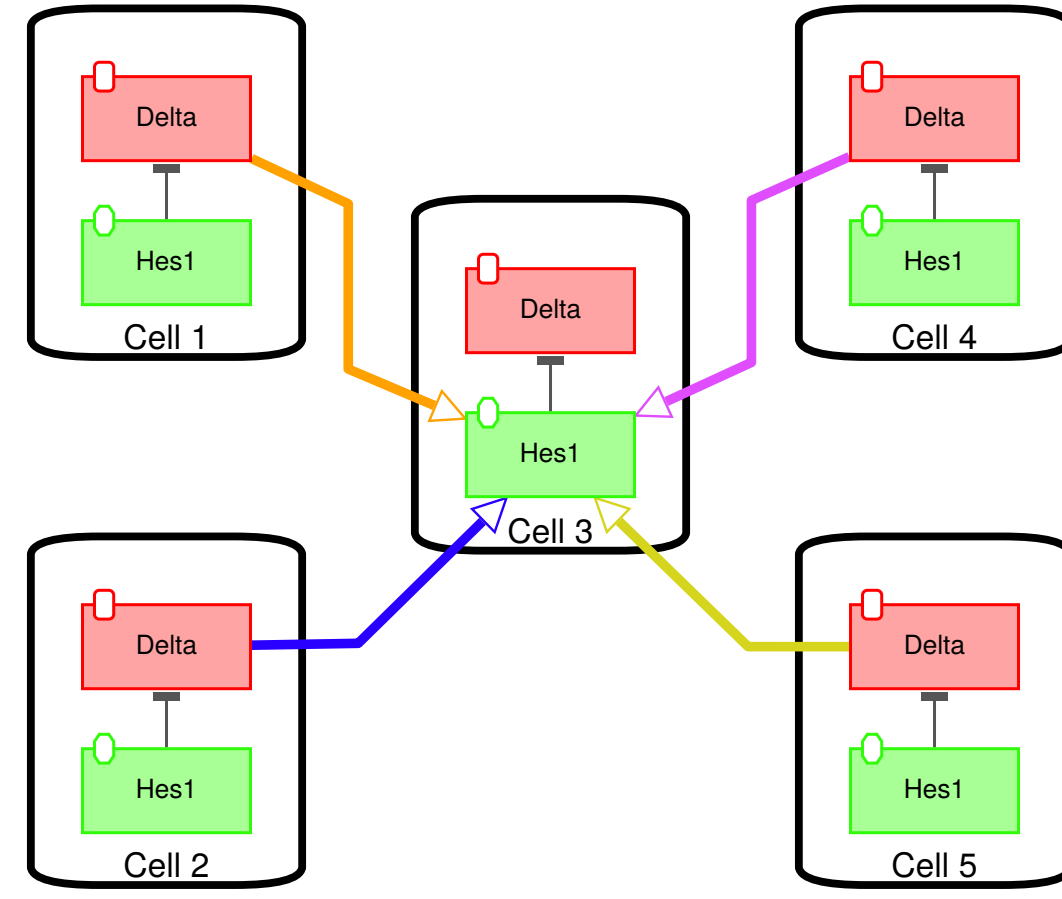


Figure 2. Delta from neighboring cells

The network representation may be implicit (population model) or explicit (graph):

- **Non-destructive measurements** allow explicit reconstruction of the network by fitting dynamic models to longitudinal data
- **Destructive measurements** require assumptions about pattern geometry to convert the explicit model to population-level representation
- **Fully Coupled Model** requires a regularized fitting scheme.
- **Regularization** is based on the assumption that a fully connected network is unlikely (also impossible in the case of juxtacrine signaling) so a *sparse representation* of the network is enforced via regularization.

Regularized Dictionary Learning

$\frac{dH1_i}{dt} = F(H1_i(t))$ is a linear combination of (trans) growth and (cis) inhibition.

$F(H1_i(t)) =$ the interpolant of $H1_i(t)$

$\Phi(d(t)) =$ Hill-type transformations over Delta protein levels

$\Psi(t) = [\Phi(d(t)), H1(t)]$

$F(H1_i(t)) \approx \Psi(t)\beta_i$

(1)

Find the cross-validated Elastic Net estimate [2] of β for each cell.

$Adj \leftarrow \text{zeros}(|Cells|)$

for cell i in Cells **do**

$\hat{\beta}_{iCV} \leftarrow \underset{\beta}{\text{argmin}} \left(|F(H1_i(t)) - \Psi(t)\beta|^2 + \lambda_2 |\beta|^2 + \lambda_1 |\beta|_1 \right)$

for cell j in Cells **do**

if $\text{sum}[\hat{\beta}_{iCV}(1 : j : \text{end})] > 0$ **then**

$Adj(i, j) = 1$

end if

end for

end for

Fate Determination: Multistability of Notch Signal and Ligand Expression

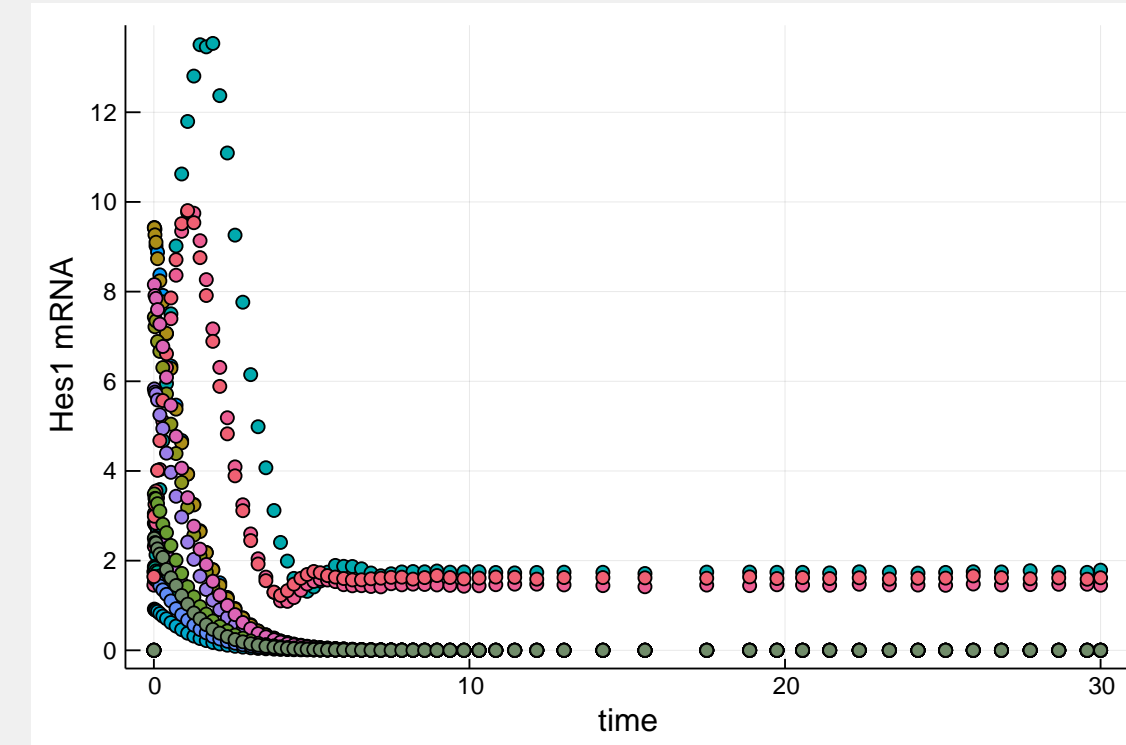


Figure 3. Notch signal

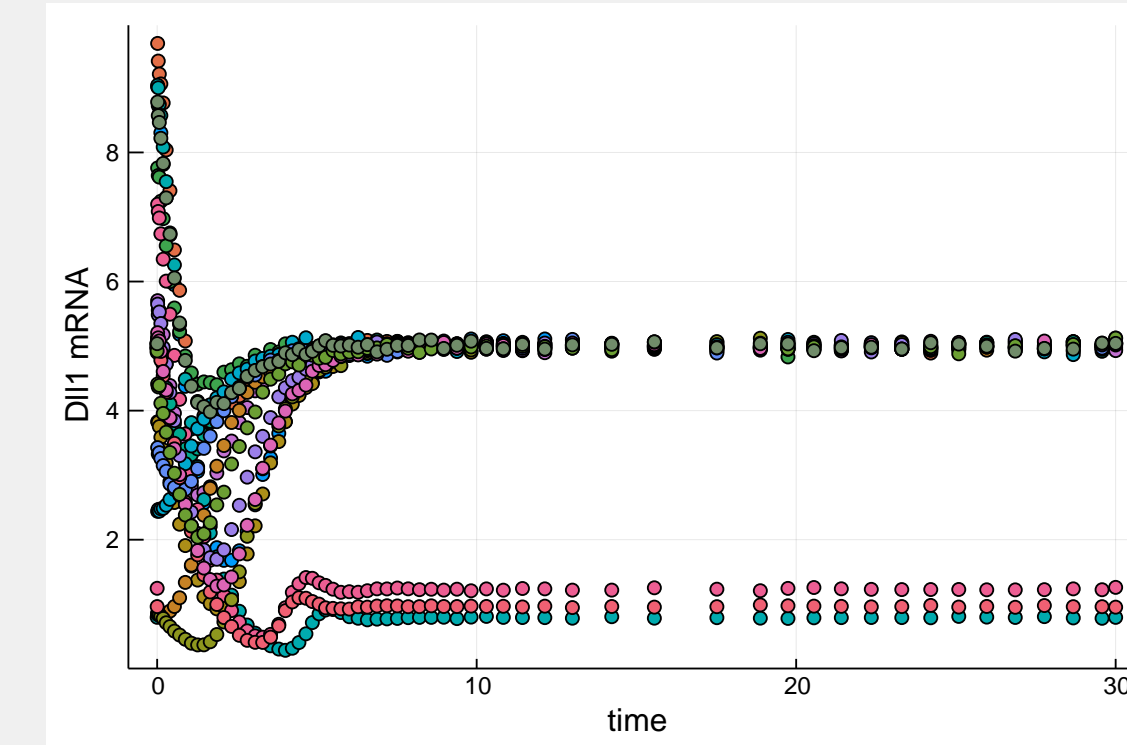


Figure 4. Dll ligand expression

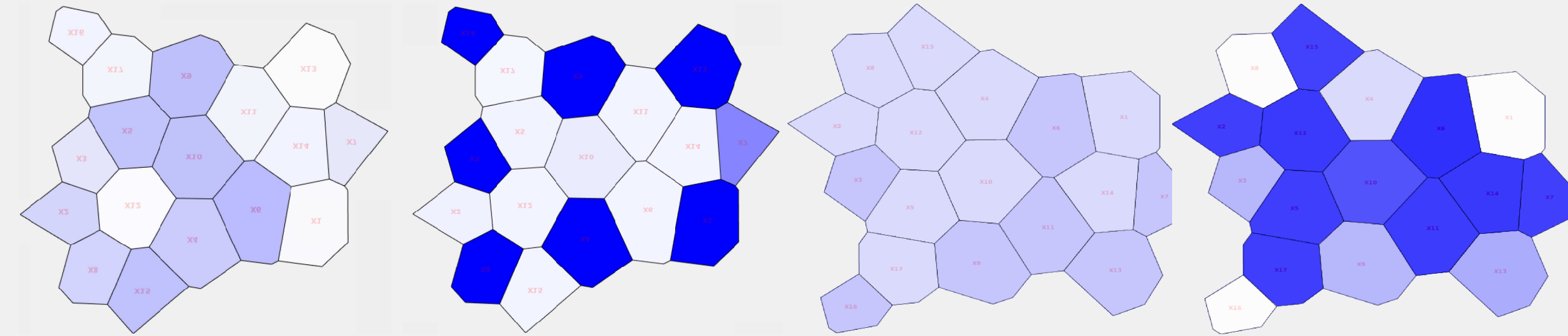


Figure 5. $\Delta_{t=1}$, $\Delta_{t=10}$, $Hes1_{t=1}$, $Hes1_{t=10}$

Simulate Non-Destructive Time Series Measurement

$$\frac{dd_i}{dt} = \nu \left(\frac{\beta_{d,i}}{1 + H1_i^h} - d_i \right) \quad (2)$$

$$\frac{dH1_i}{dt} = \sum_{j \neq i}^{\Gamma(i)} \frac{\beta_{H1,i} \Delta d_j^m}{1 + \Delta d_j^m} - H1_i \quad (3)$$

Symbol	Description	Value
d_i	Delta protein	
$H1_i$	Hes1 protein	
$H1_i^{obs}$	Hes1 protein, noisy observation: $\mathcal{N}(\gamma H1_i(t), 0.1)$	
γ	scaling for Gaussian noise on $H1_i^{obs}$	0.01-0.1
$d_i(0), H1_i(0)$	randomly perturbed initial state	
$\beta_{d,i}$	intrinsic Delta ligand production	5
$\beta_{H1,i}$	trans-activation strength	20
Δ	scaled shared cell membrane for unit grid tessellation	0-1
m, h	activation and repression cooperativity	3, 3
ν	timescale ratio: repressor/ligand dynamics	1
t	unitless time	1:30 (model fitted on 1:15)
$\Gamma(i)$	neighbors of cell i	

Accuracy of the Explicit Solution

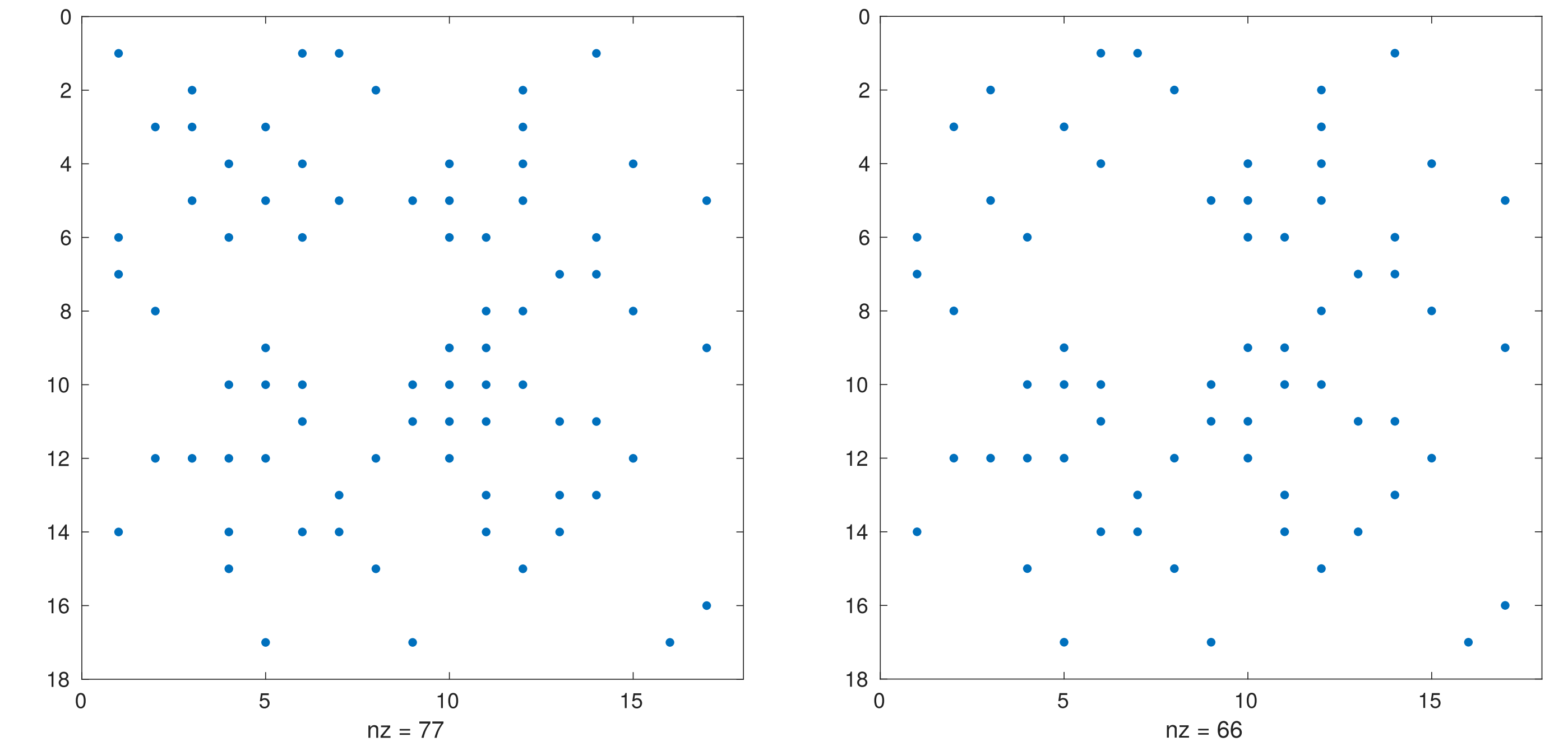


Figure 6. True adjacency vs. Estimated adjacency ($\alpha = 1, \gamma = 0.01$)

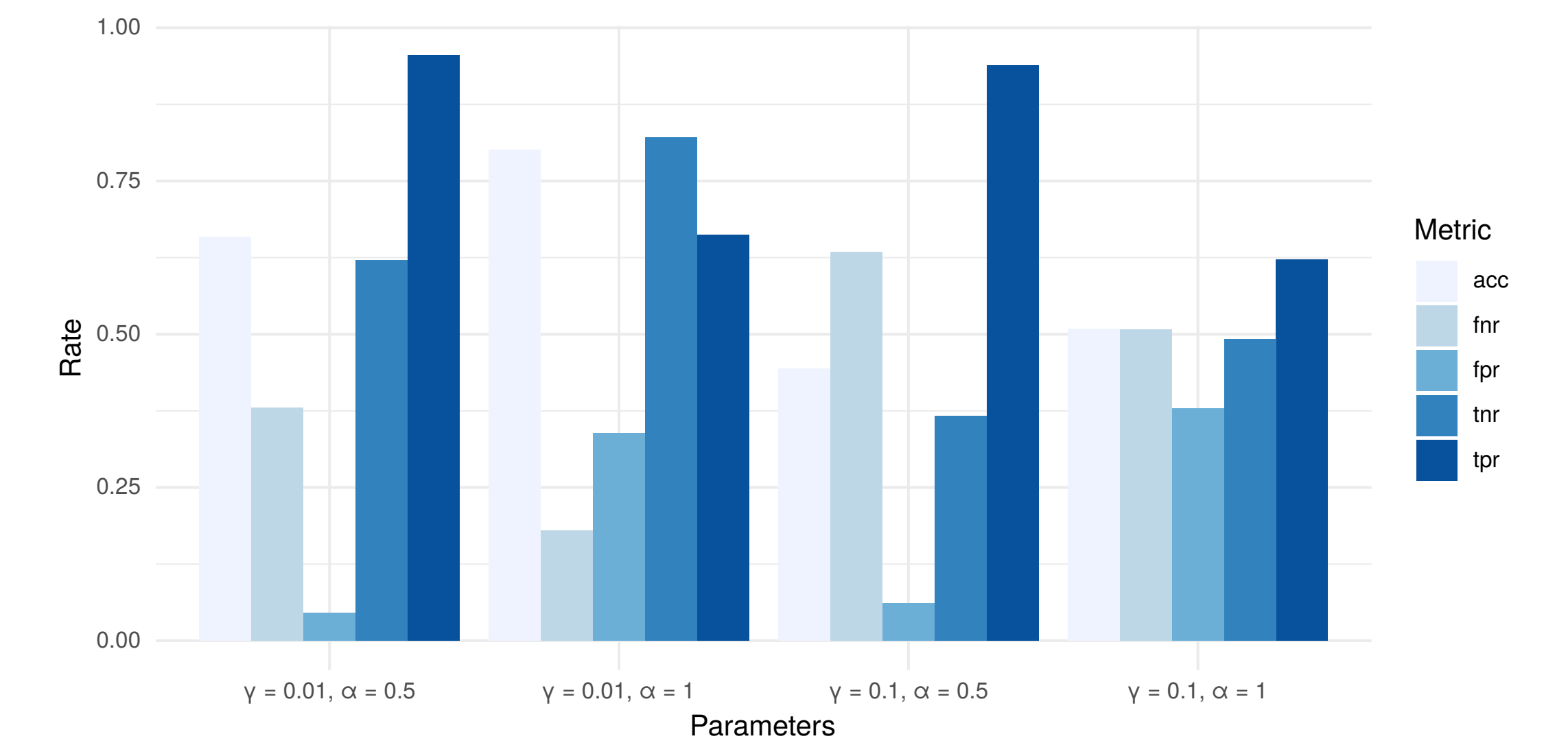


Figure 7. Classification accuracy for $\Psi(d(t)) = \left[H1(t), \frac{d^3}{1+d^3}, \frac{d^4}{1+d^4} \right]$

References

- [1] O Shaya and D Sprinzak. From Notch signaling to fine-grained patterning: Modeling meets experiments. *Current Opinion in Genetics & Development*, 21(6):732–739, December 2011.
- [2] Hui Zou and Trevor Hastie. Regularization and variable selection via the elastic net. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 67(2):301–320, April 2005.