Experimental verification of a coarse-grained model of mRNA localization reveals robustness regulated via crowding

Jonathan U. Harrison, Richard M. Parton, Ilan Davis, Ruth E. Baker

BIRS, Banff 15th November 2018

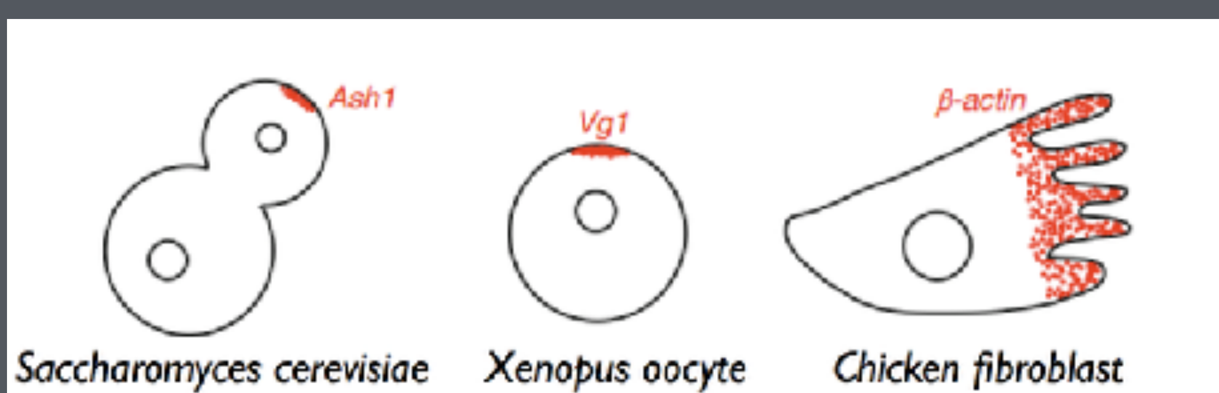
@jonty3502

University of Oxford Mathematical Institute

Oxford Mathematics

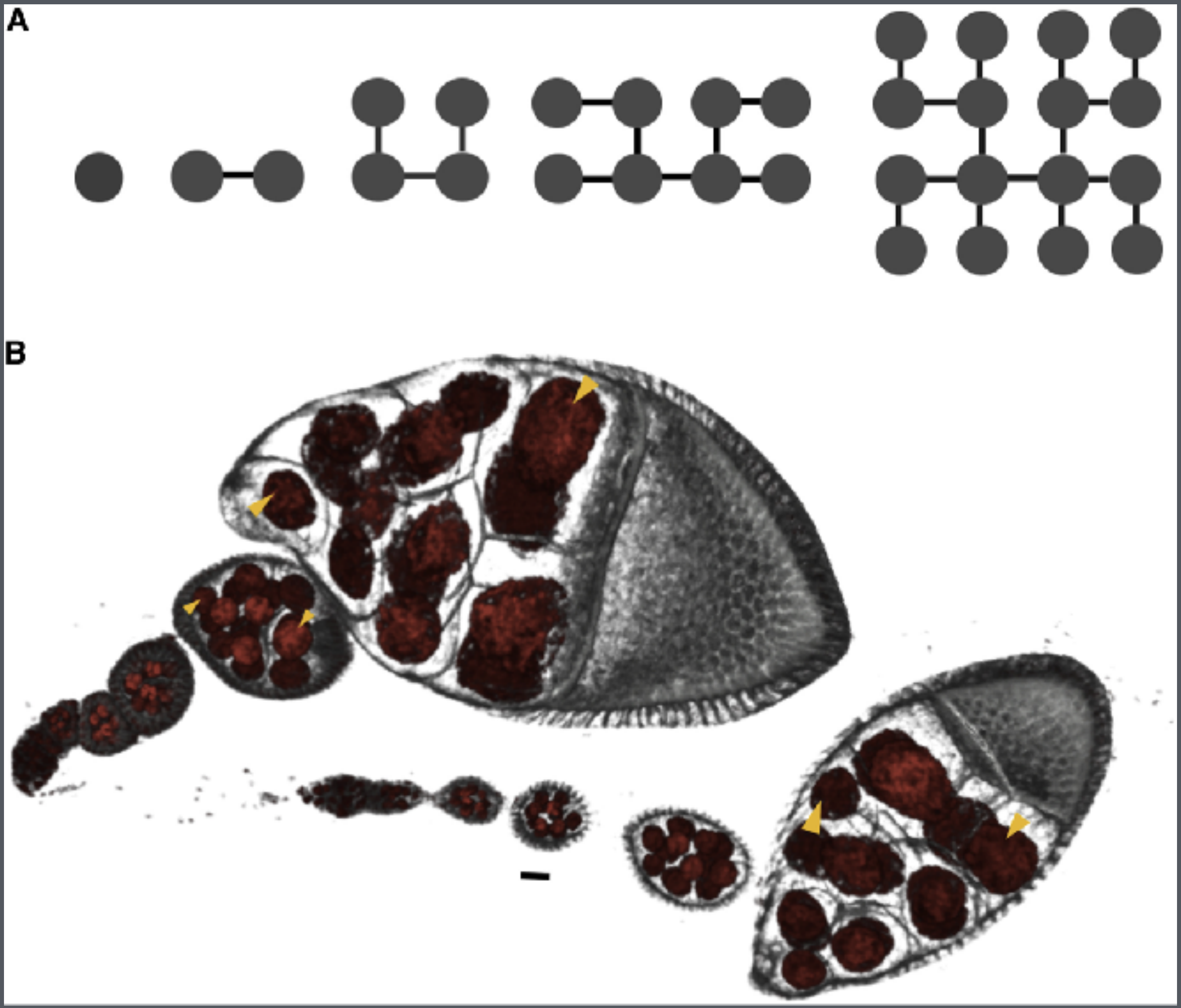
Post-transcriptional regulation of mRNA

- Many cell types use post-transcriptional regulation of mRNA to target proteins precisely in space and time
- mRNA localization is key in establishment of the body axis, cell migration, synaptic plasticity



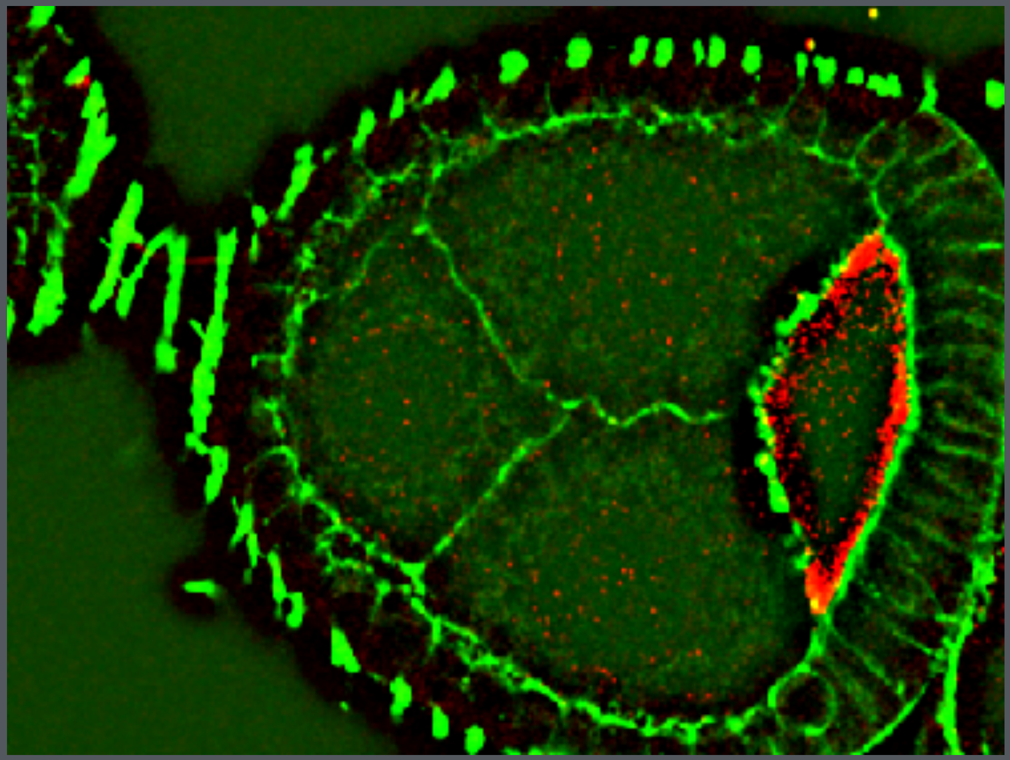
- What controls mRNA localization?
  - What ensures mRNA localization is so robust?
  - What biological mechanisms regulate this robustness?

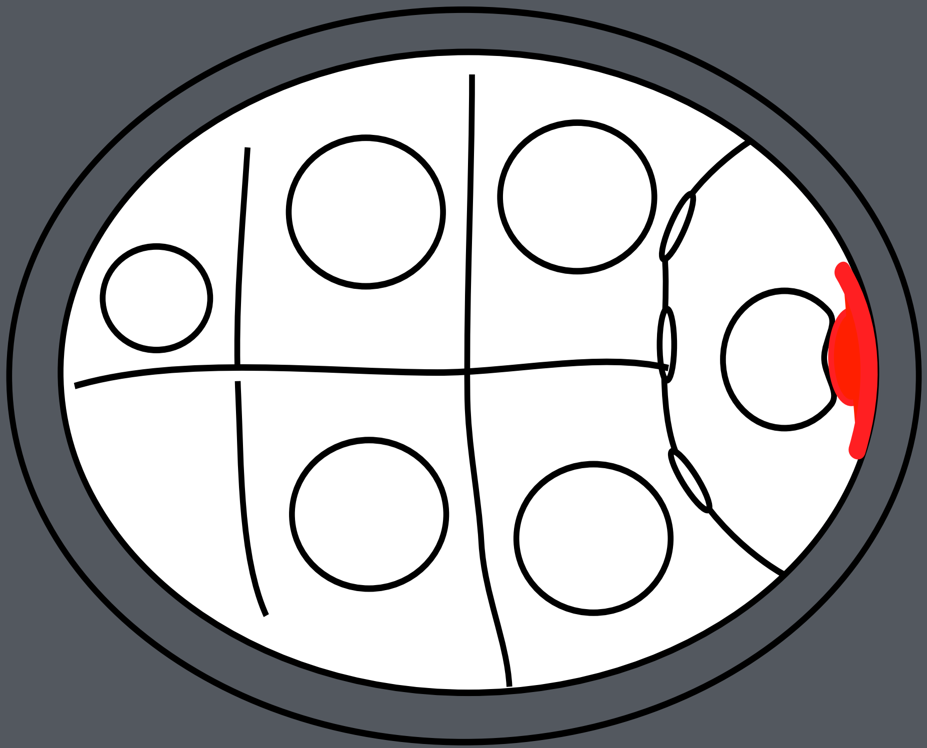
Drosophila egg chambers have a characteristic pattern of connections between cells



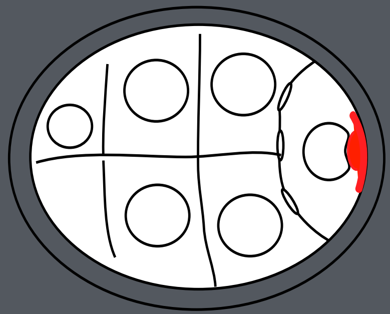
Alsous, Jasmin Imran, Paul Villoutreix, Alexander M. Berezhkovskii, and Stanislav Y. Shvartsman. "Collective growth in a small cell network." Current Biology 27, no. 17 (2017): 2670-2676.

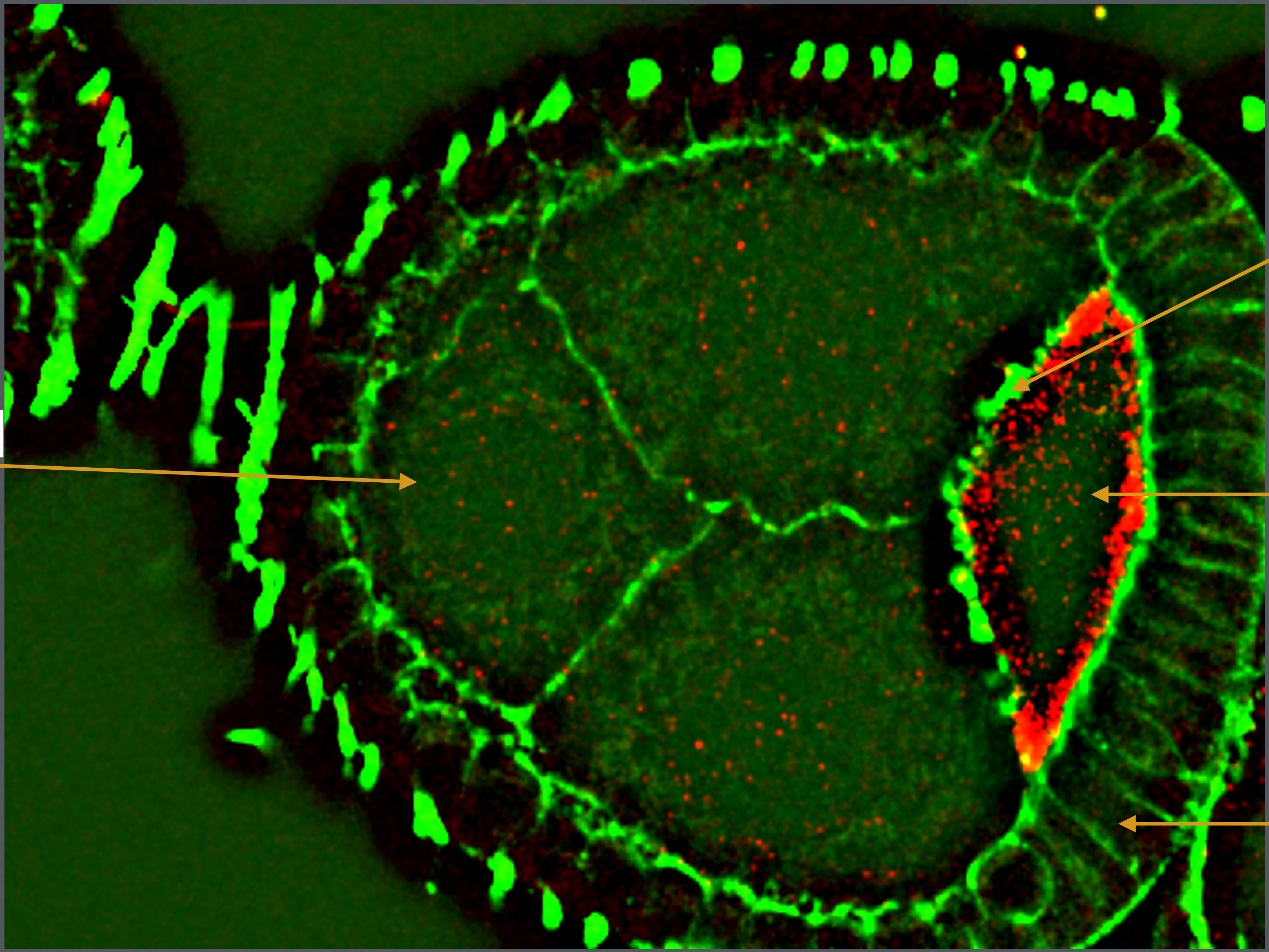
Localization of mRNA in *Drosophila* egg chambers



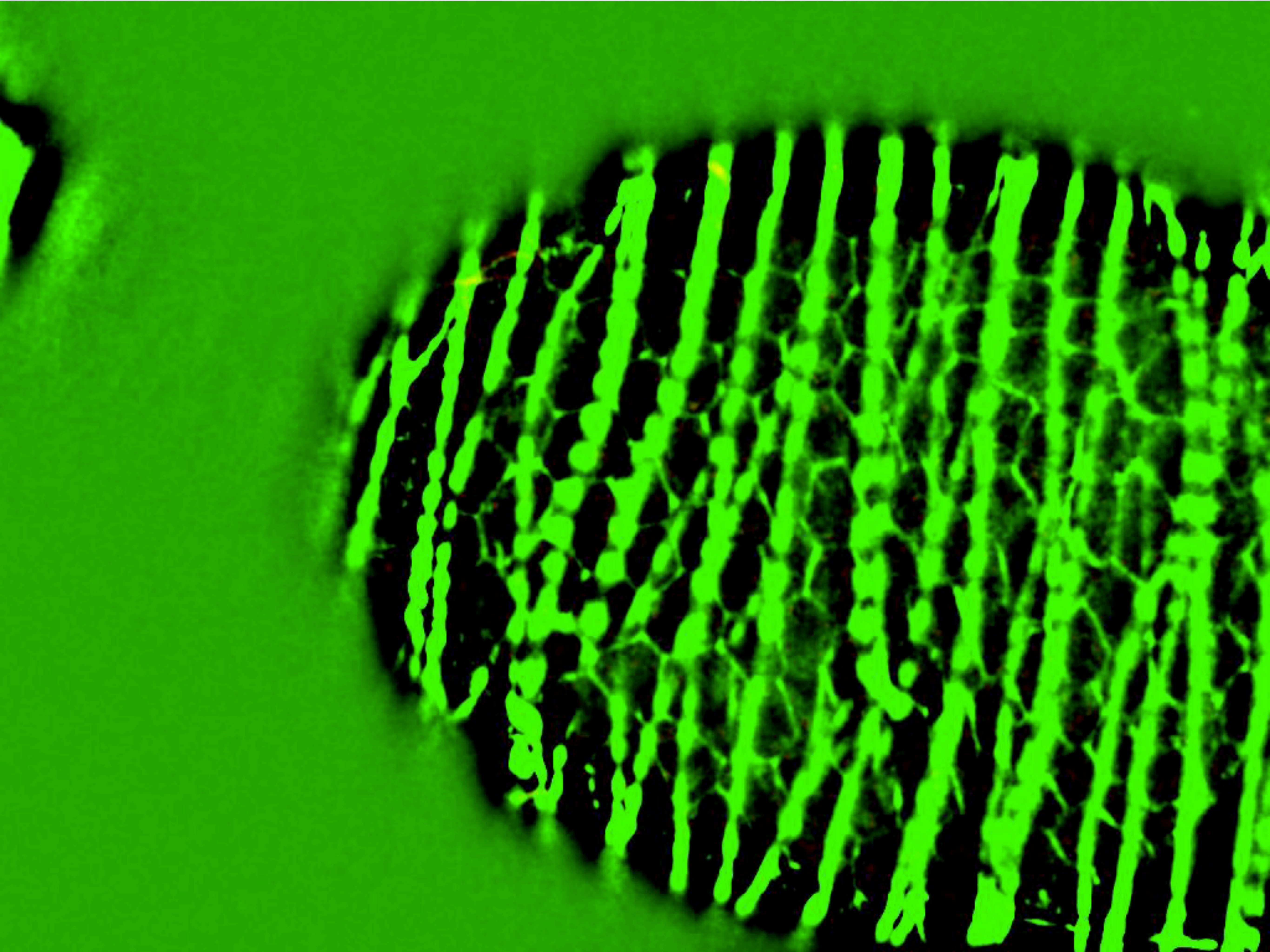


- In oogenesis, mRNAs are transported from the maternal nurse cells to the oocyte
- Nurse cells are connected by ring canals

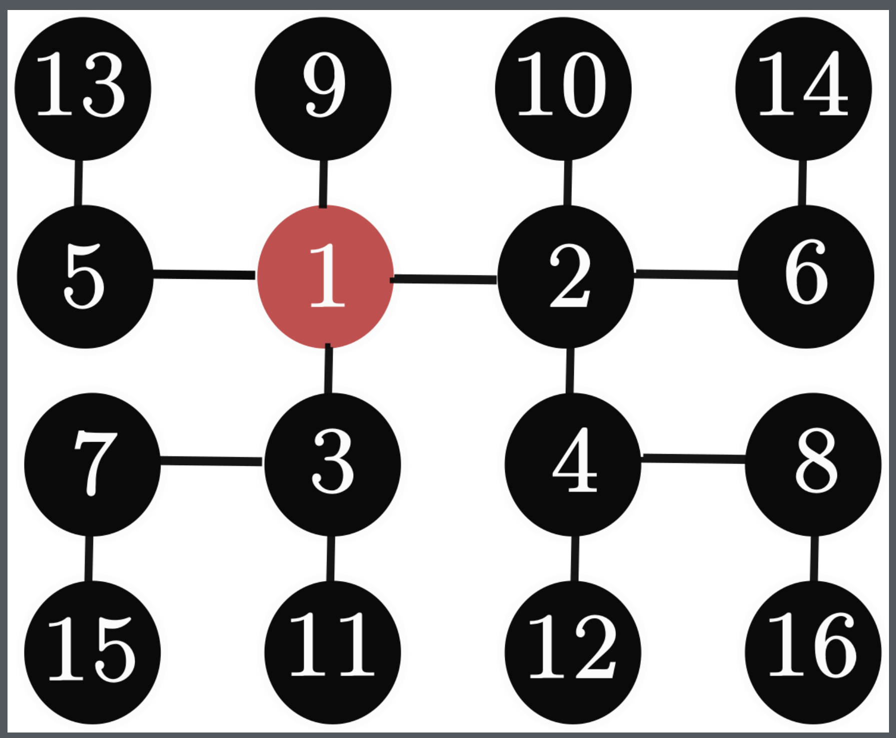


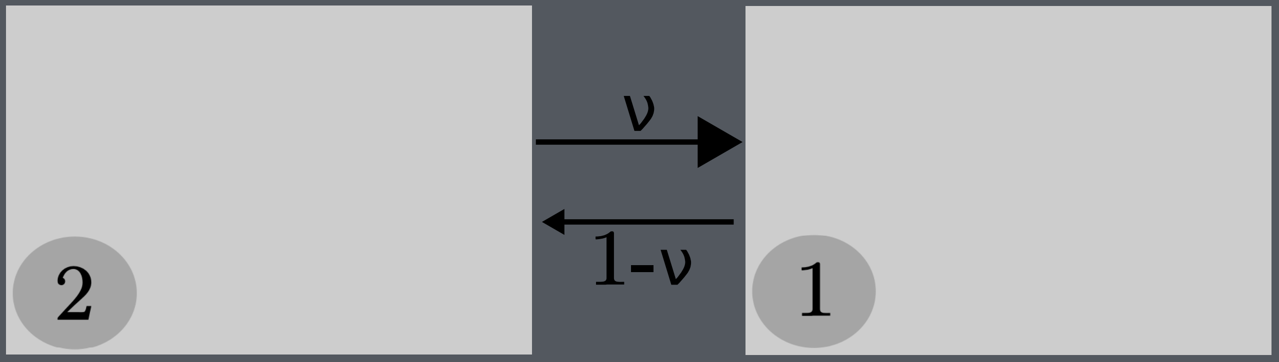


Moesin GFP
grk mRNA

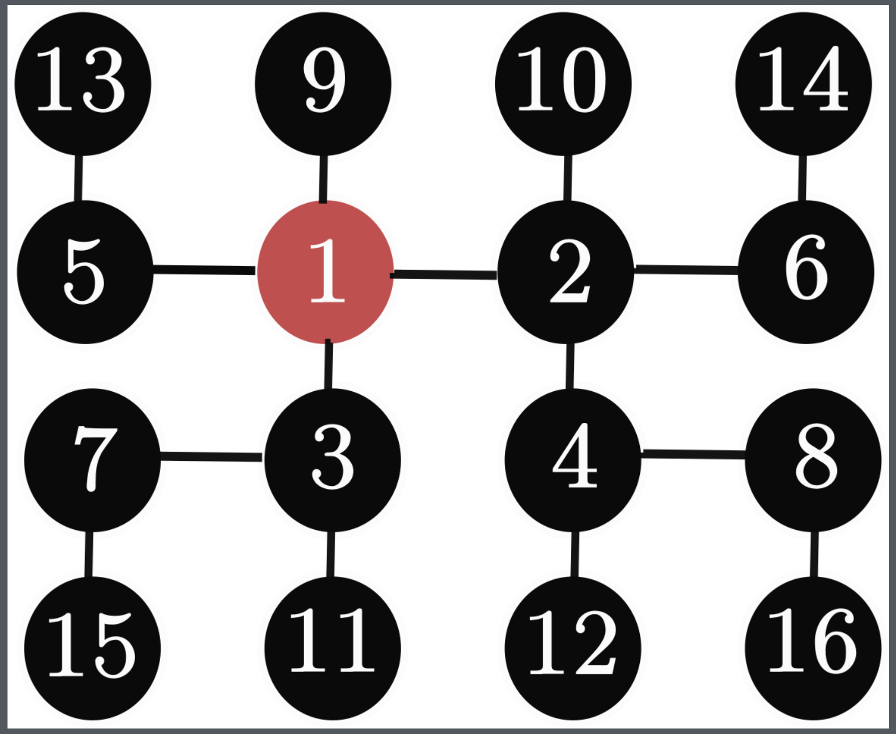


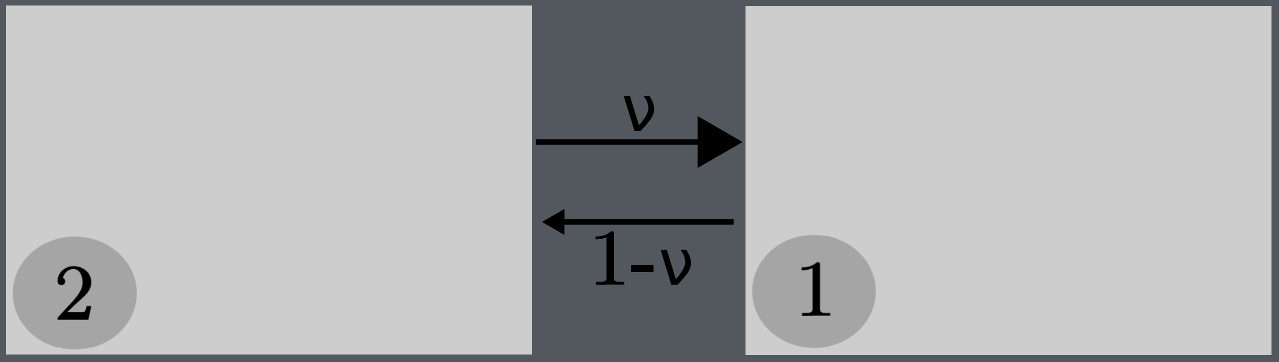
Connectivity between cells can be characterised due to ring canals





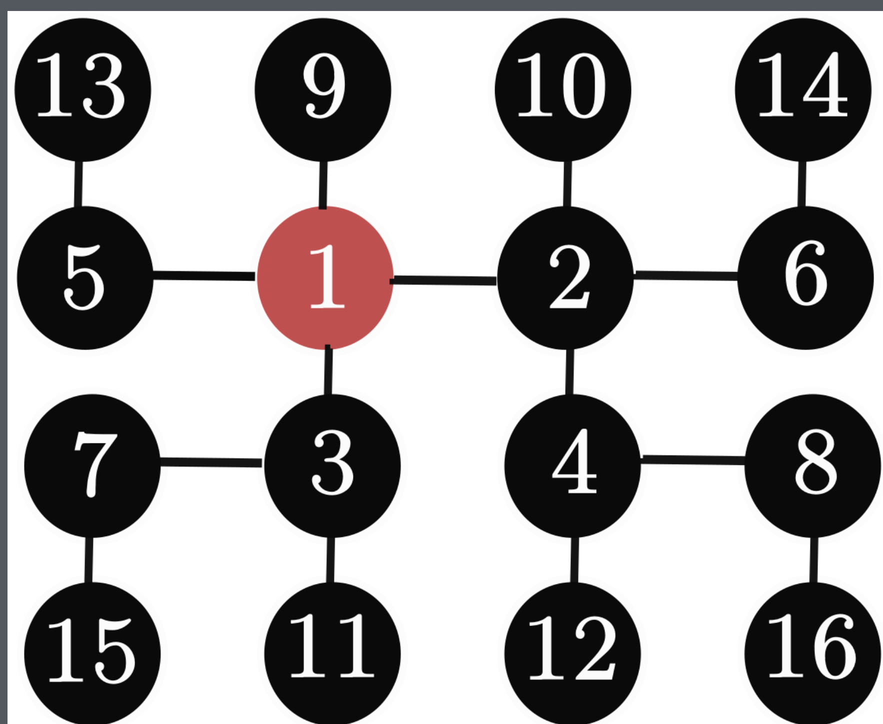
Connectivity between cells can be characterised due to ring canals

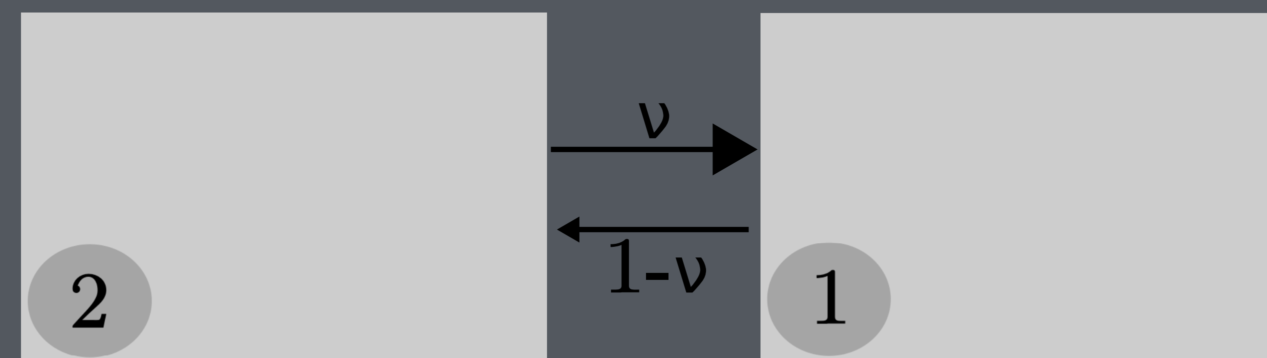




- Simple compartment-based ODE model
- Production in each cell
- Transport between cells connected by a ring canal

Connectivity between cells can be characterised due to ring canals





$$B = \begin{pmatrix}
-4+4\nu & \nu & \nu & 0 & \nu & 0 & 0 & 0 & \nu & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
1-\nu & -3+2\nu & 0 & \nu & 0 & \nu & 0 & 0 & 0 & \nu & 0 & 0 & 0 & 0 & 0 & 0 \\
1-\nu & 0 & -2+\nu & 0 & 0 & 0 & \nu & 0 & 0 & 0 & \nu & 0 & 0 & 0 & 0 & 0 \\
0 & 1-\nu & 0 & -2+\nu & 0 & 0 & 0 & \nu & 0 & 0 & 0 & \nu & 0 & 0 & 0 & 0 \\
1-\nu & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \nu & 0 & 0 & 0 \\
0 & 1-\nu & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \nu & 0 & 0 \\
0 & 0 & 1-\nu & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \nu & 0 \\
0 & 0 & 0 & 1-\nu & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \nu \\
1-\nu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\nu & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1-\nu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\nu & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1-\nu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\nu & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1-\nu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\nu & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1-\nu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\nu & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1-\nu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\nu & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1-\nu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\nu & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1-\nu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\nu
\end{pmatrix}$$

Coarse-grained model

$$\frac{d\mathbf{y}}{dt} = a\,\mathbf{v} + b\,\mathbf{B}(\nu)\,\mathbf{y}$$

mRNA production at rate *a*

mRNA transport at rate *b*

Coarse-grained model

$$\frac{d\mathbf{y}}{dt} = a\,\mathbf{v} + b\,\mathbf{B}(\nu)\,\mathbf{y}$$

$$\mathbf{y} = VD\mathbf{c} + \mathbf{k_1} + 15a\mathbf{k_2}t$$

Effect of initial condition

Constant term

Quasi-steady-state linear increase

Bayesian inference framework

Measurement model $\mathbf{z} \sim NB(\Phi\mathbf{y}, \sigma)$

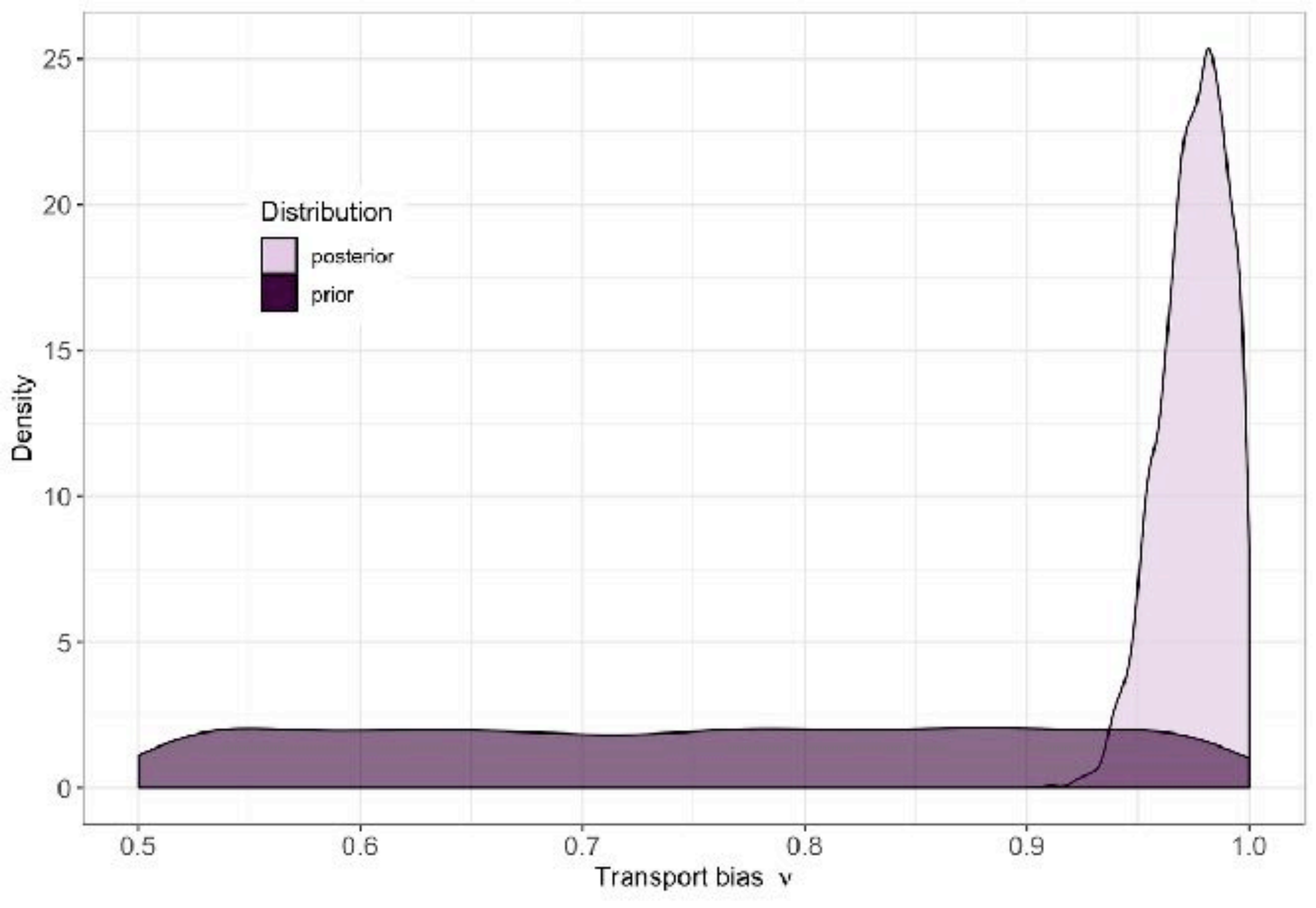
where Φ has diagonal entries $[\phi, 1, \ldots, 1]$

Bayesian inference allows us to propagate forward uncertainties in measurement and incorporate expert knowledge

Sample from posterior distribution $p(\theta \mid \mathbf{z})$ via MCMC (Hamiltonian Monte Carlo)

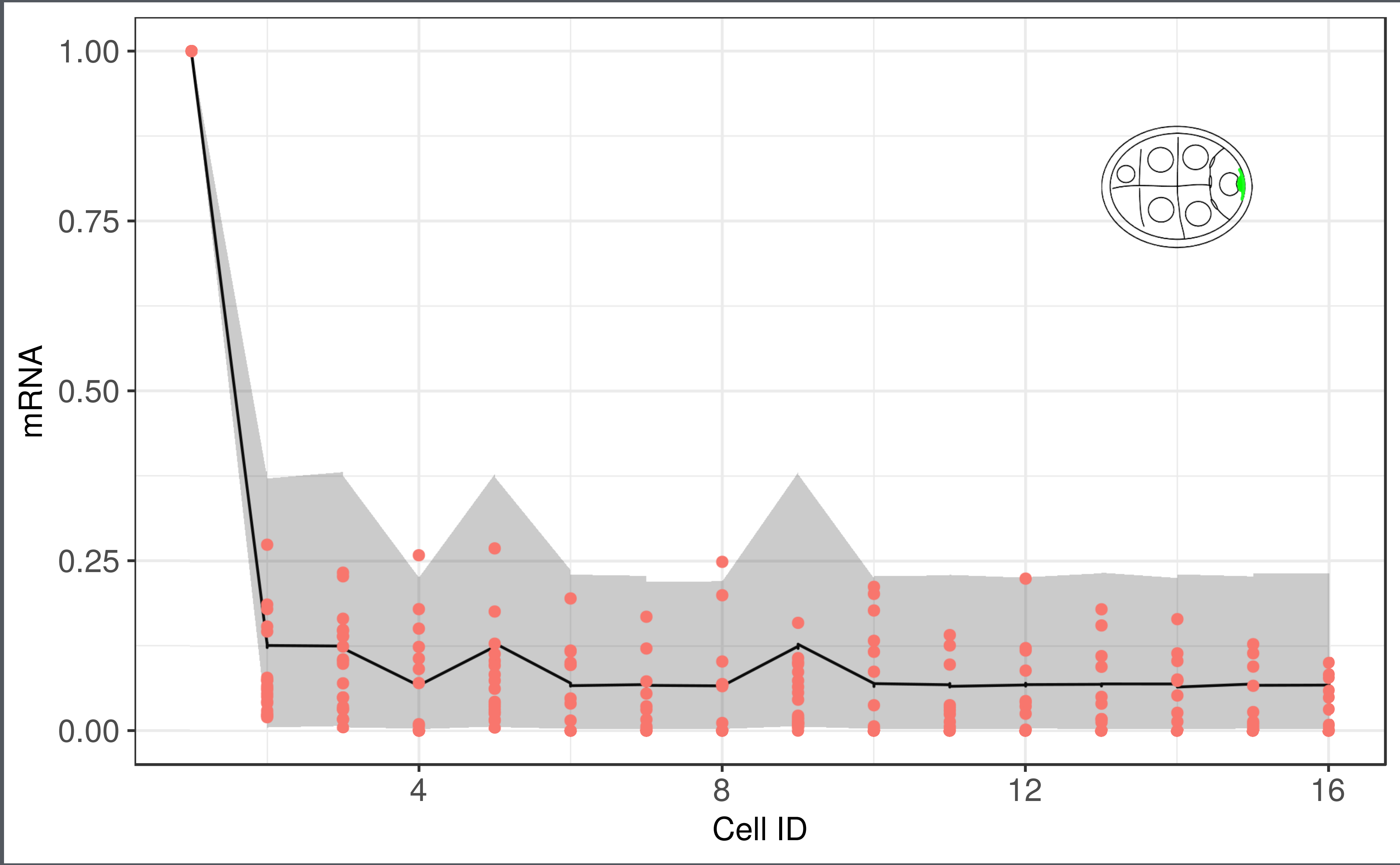
Stan http://mc-stan.org/

Results at steady state show transport through ring canals is strongly biased



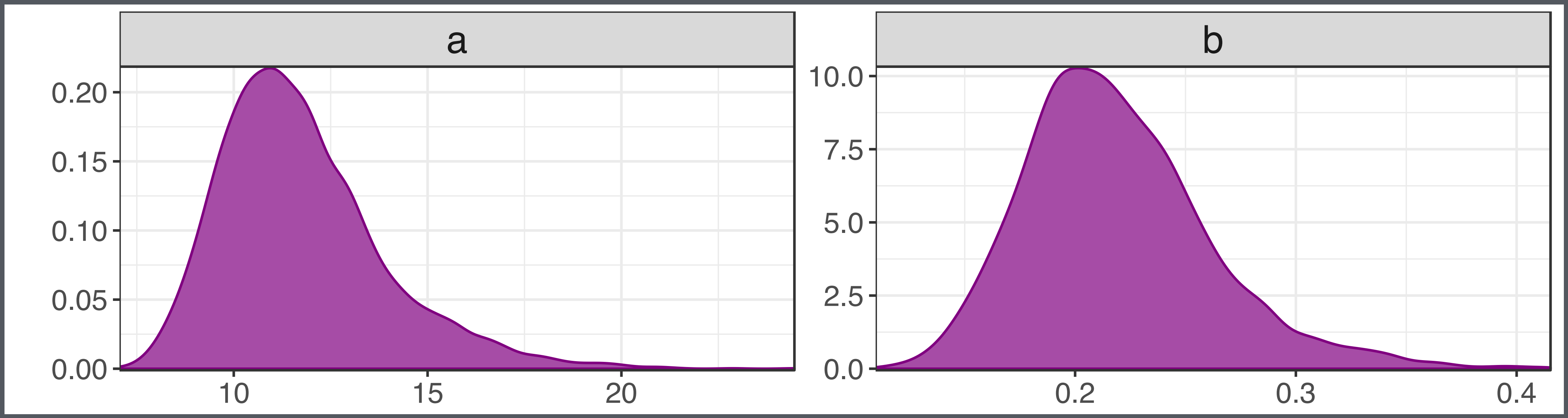
95% credible interval for ν of [0.94,1.00]

Results at steady state show transport through ring canals is strongly biased



95% credible interval for ν of [0.94,1.00]

Results in dynamic regime suggest production and transport are carefully balanced



95% credible intervals:

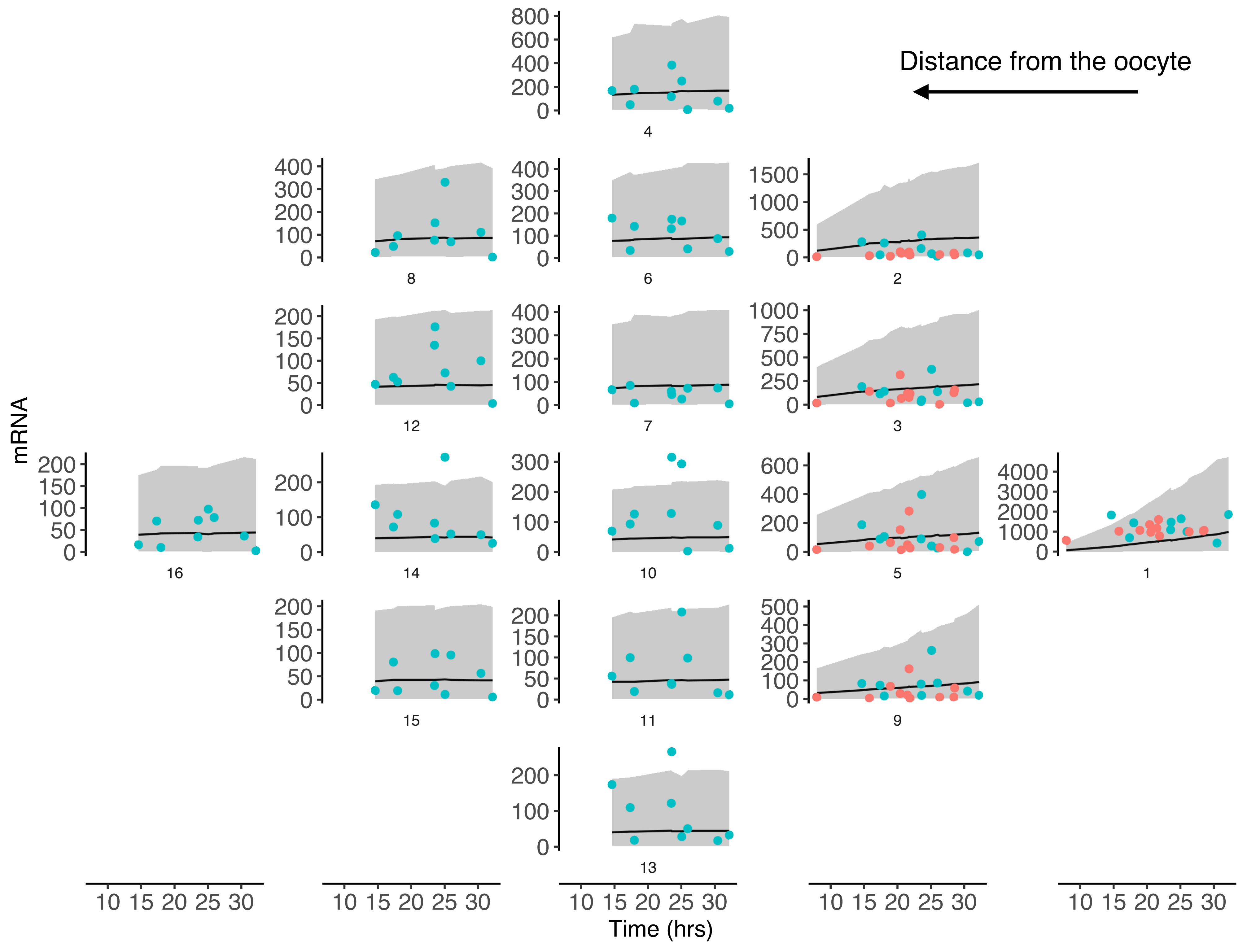
a [9.5, 18.9] particles hr^{-1}

b [0.16, 0.35] hr^{-1}

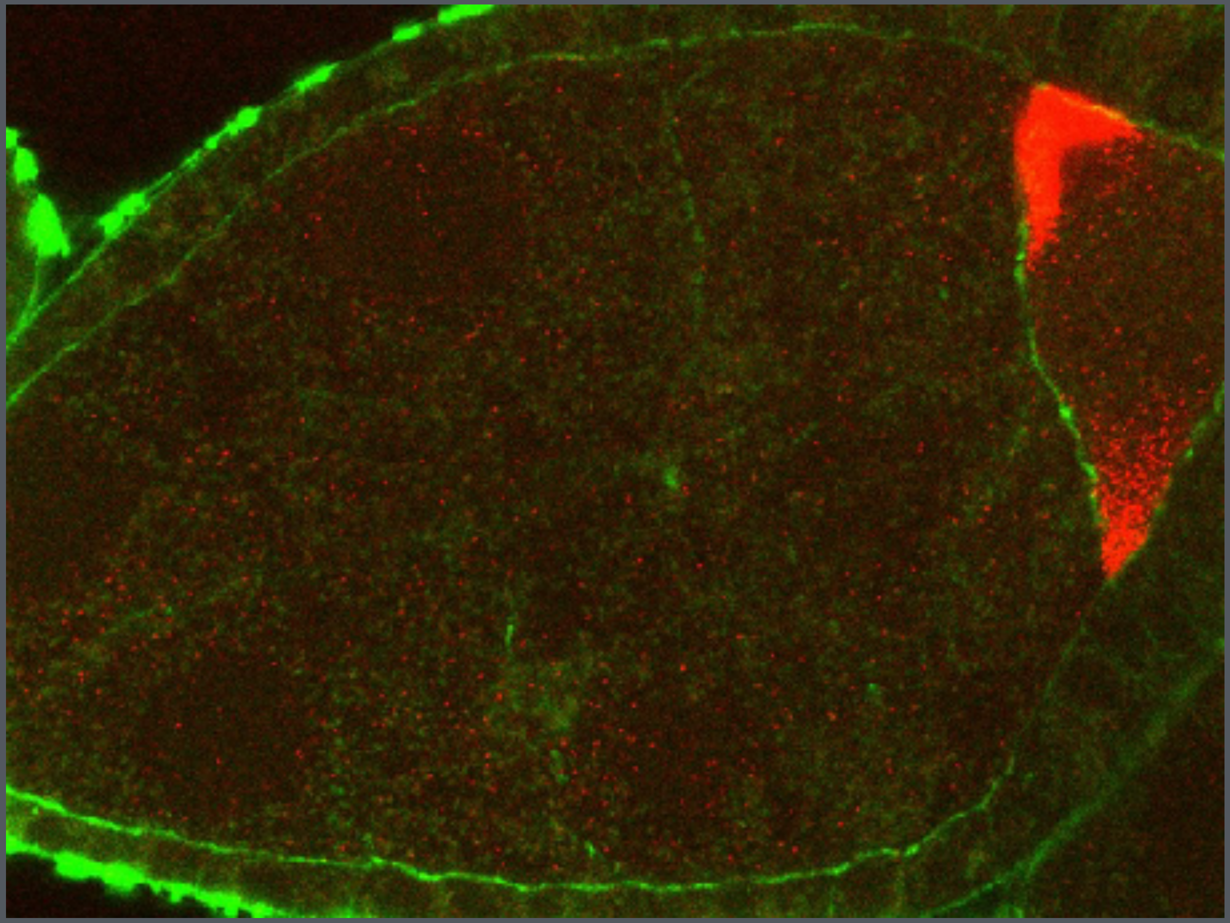
Scaling to comparable units shows production and transport are balanced

$$a \approx b\langle \tilde{\mathbf{y}} \rangle$$

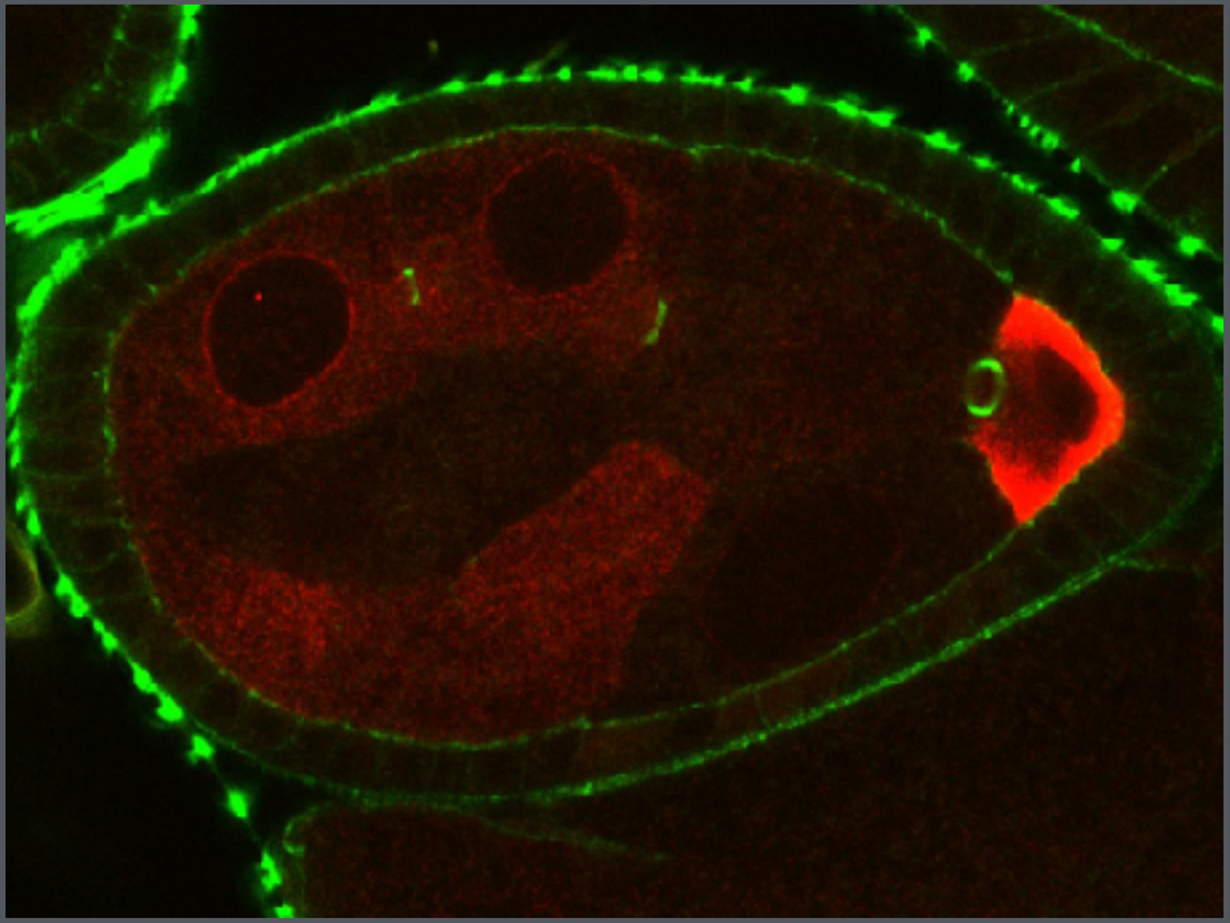
Posterior predictions from the model



Prediction of behaviour for *gurken* overexpression



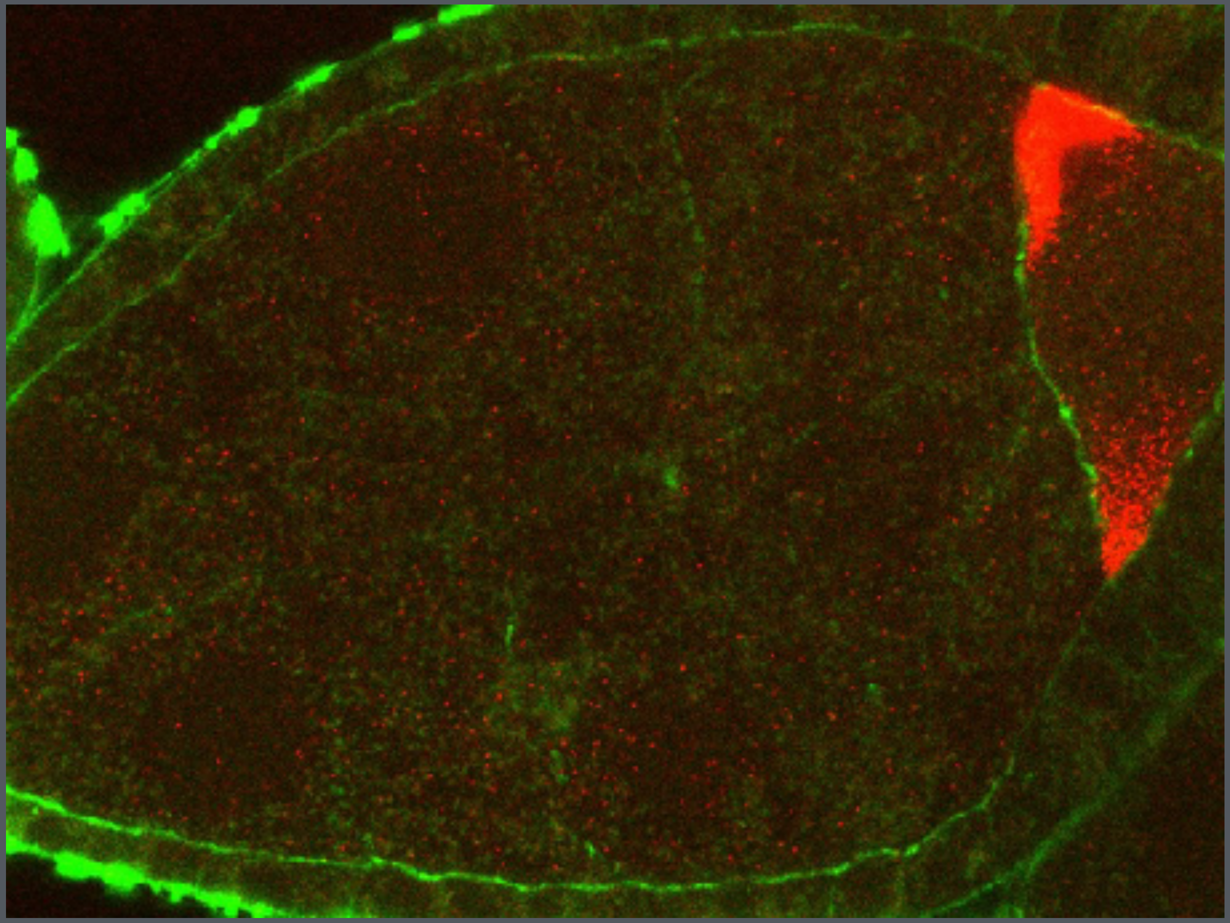
WT



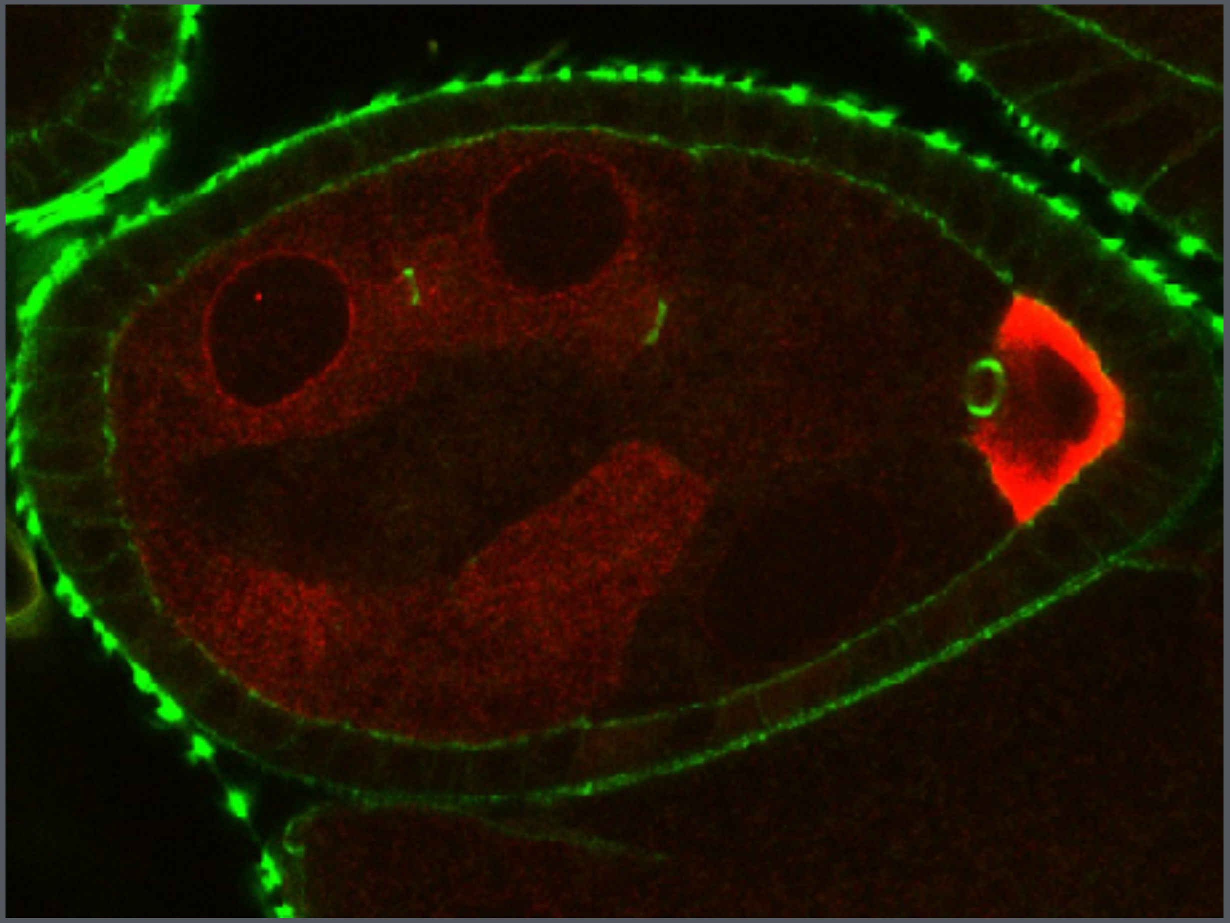
Overexpressor

Prediction of behaviour for *gurken* overexpression

$$\frac{d\mathbf{y}}{dt} = 2a\,\mathbf{v} + b\,\mathbf{B}(\nu)\,\mathbf{y}$$

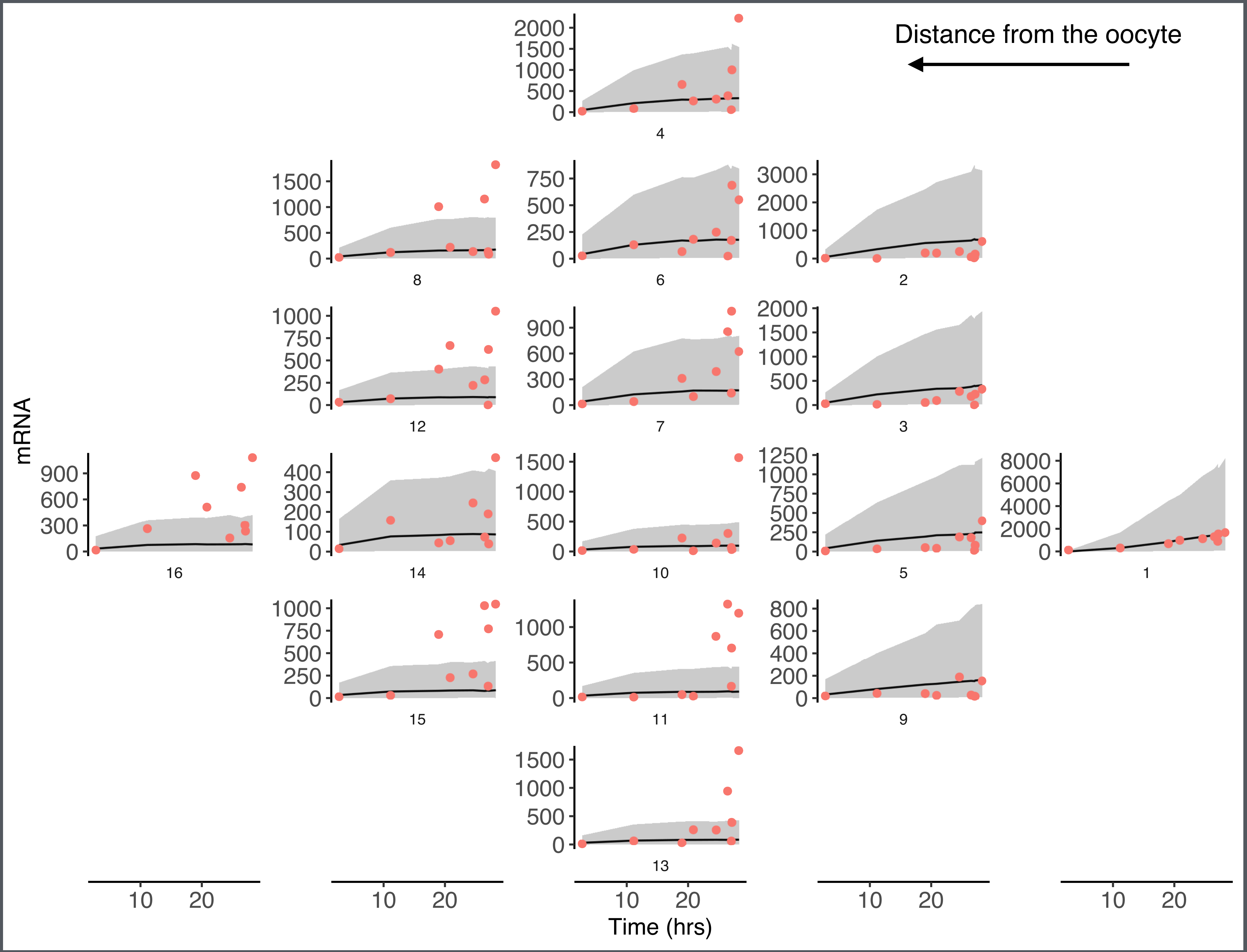


WT

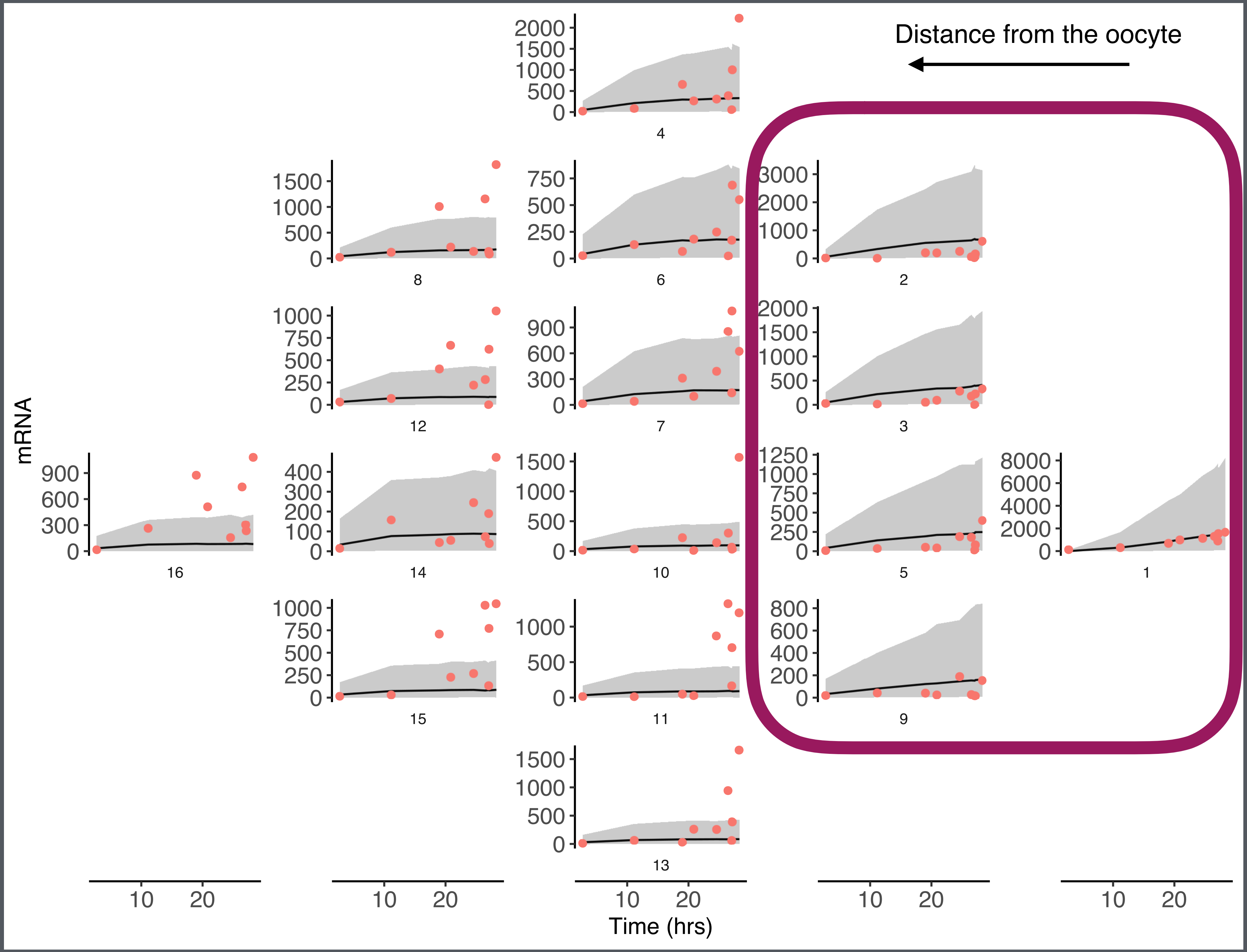


Overexpressor

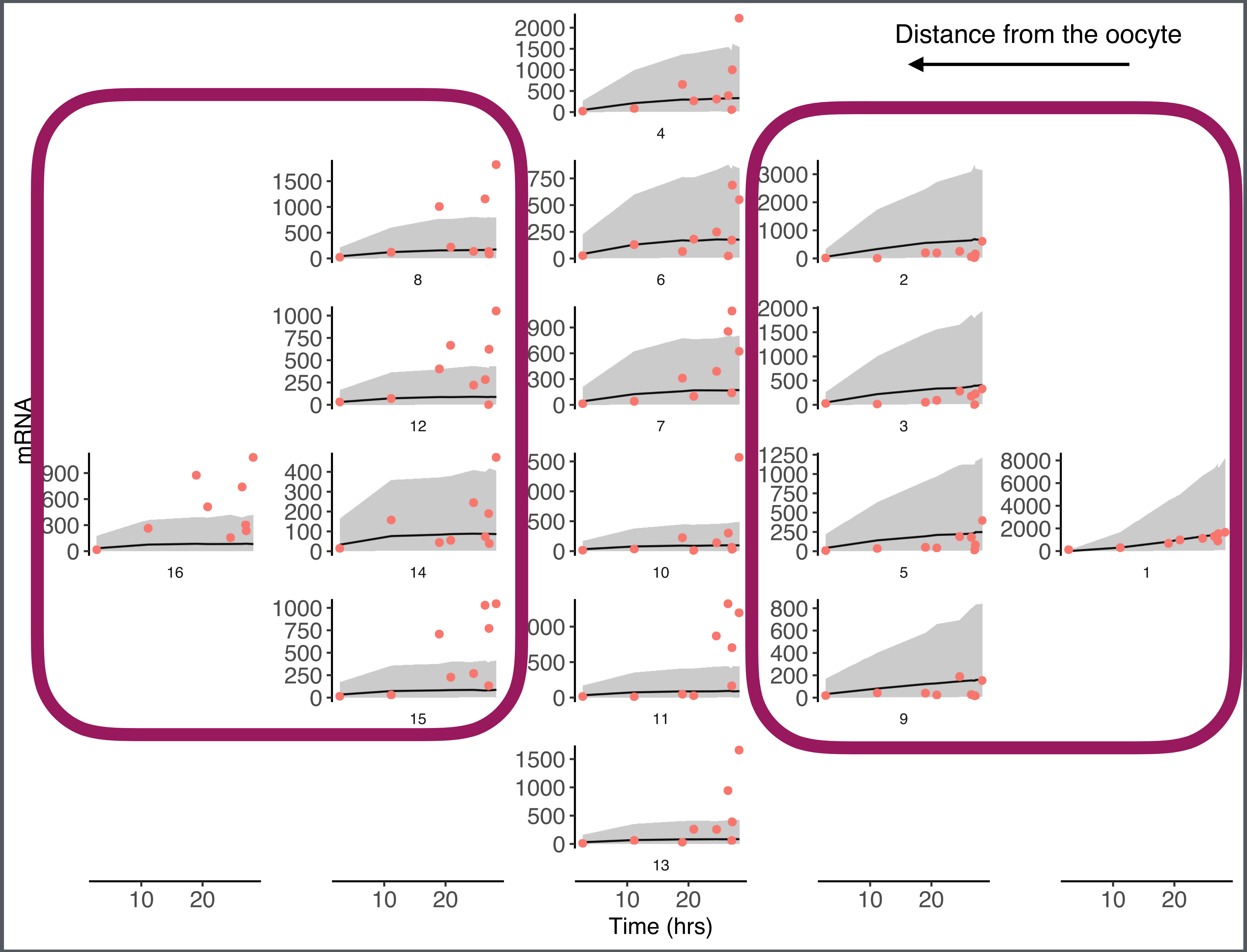
Prediction of behaviour for *gurken* overexpressor



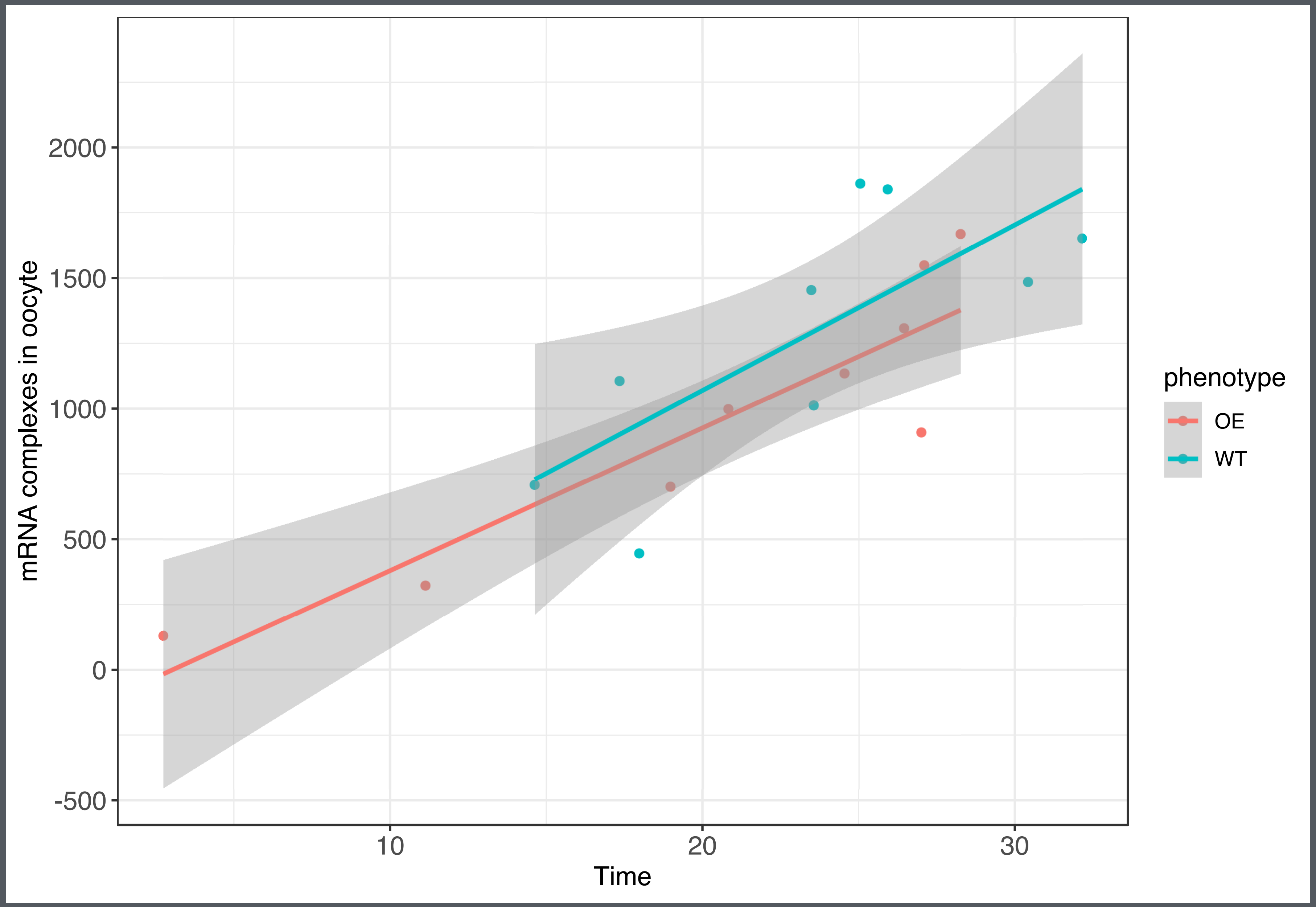
Prediction of behaviour for *gurken* overexpressor



Prediction of behaviour for *gurken* overexpressor



Localization of RNA in oocyte of the overexpression mutant reveals robustness



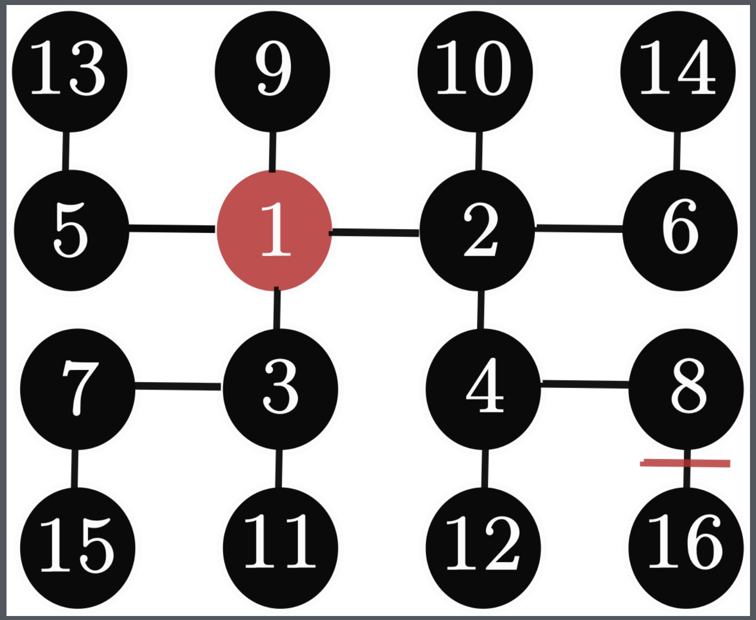
Why don’t the predictions agree?

1. Blocking of ring canals
2. Inhomogeneous production
3. Density dependent transport

Why don't the predictions agree?

1. Blocking of ring canals

Alter entries of matrix B to remove connections between certain cells



Why don't the predictions agree?

2. Inhomogeneous production

Production of RNA in nuclei of different cells may vary in the OE mutant due to the GAL4-UAS system used to drive the mutation

Estimate $a\mathbf{v}$ based on nascent transcription data

Why don't the predictions agree?

3. Density dependent transport

Previously assumed transport was linear in the amount of RNA in a nurse cell

$$b\,y$$

But due to availability of molecular motors, transport may saturate

$$b\,f(y) \quad \text{where} \quad f(y) = \frac{y}{1+\beta y}$$

Model comparison

Expected log predictive density (elpd)

$$\mathbb{E}\left[\log\left(\int p(y^{OE}\,|\,\theta)p(\theta\,|\,y^{WT})\,d\theta\right)\right] \approx \frac{1}{n}\sum_{i=1}^{n}\log\left(\int p(y_i^{OE}\,|\,\theta)p(\theta\,|\,y^{WT})\,d\theta\right)$$

Model comparison

Expected log predictive density (elpd)

$$\mathbb{E}\left[\log\left(\int p(y^{OE}|\theta)p(\theta|y^{WT})\,d\theta\right)\right] \approx \frac{1}{n}\sum_{i=1}^{n}\log\left(\int p(y_i^{OE}|\theta)p(\theta|y^{WT})\,d\theta\right)$$

Pseudo-BMA weighting for model k

$$w_k = \frac{\exp(\textbf{elpd}_k)}{\sum_{k=1}^{K}\exp(\textbf{elpd}_k)}$$

Model comparison

Expected log predictive density (elpd)

$$\mathbb{E}\left[\log\left(\int p(y^{OE}\,|\,\theta)p(\theta\,|\,y^{WT})\,d\theta\right)\right] \approx \frac{1}{n}\sum_{i=1}^{n}\log\left(\int p(y_i^{OE}\,|\,\theta)p(\theta\,|\,y^{WT})\,d\theta\right)$$

Pseudo-BMA weighting for model k

$$w_k = \frac{\exp(\textbf{elpd}_k)}{\sum_{k=1}^{K}\exp(\textbf{elpd}_k)}$$

Stacking weights

$$\max_{w}\frac{1}{n}\sum_{i=1}^{n}\log\left(\sum_{k=1}^{K} w_k p(y_i^{OE}\,|\,y^{WT}, M_k)\right) \ \textbf{subject to}\ w_k \geq 0,\ \sum_{k=1}^{K} w_k = 1$$

Model comparison

Expected log predictive density (elpd)

$$\mathbb{E}\left[\log\left(\int p(y^{OE}\,|\,\theta)p(\theta\,|\,y^{WT})\,d\theta\right)\right] \approx \frac{1}{n}\sum_{i=1}^{n}\log\left(\int p(y_i^{OE}\,|\,\theta)p(\theta\,|\,y^{WT})\,d\theta\right)$$

Pseudo-BMA weighting for model k

$$w_k = \frac{\exp(\mathbf{elpd}_k)}{\sum_{k=1}^{K}\exp(\mathbf{elpd}_k)}$$

Stacking weights

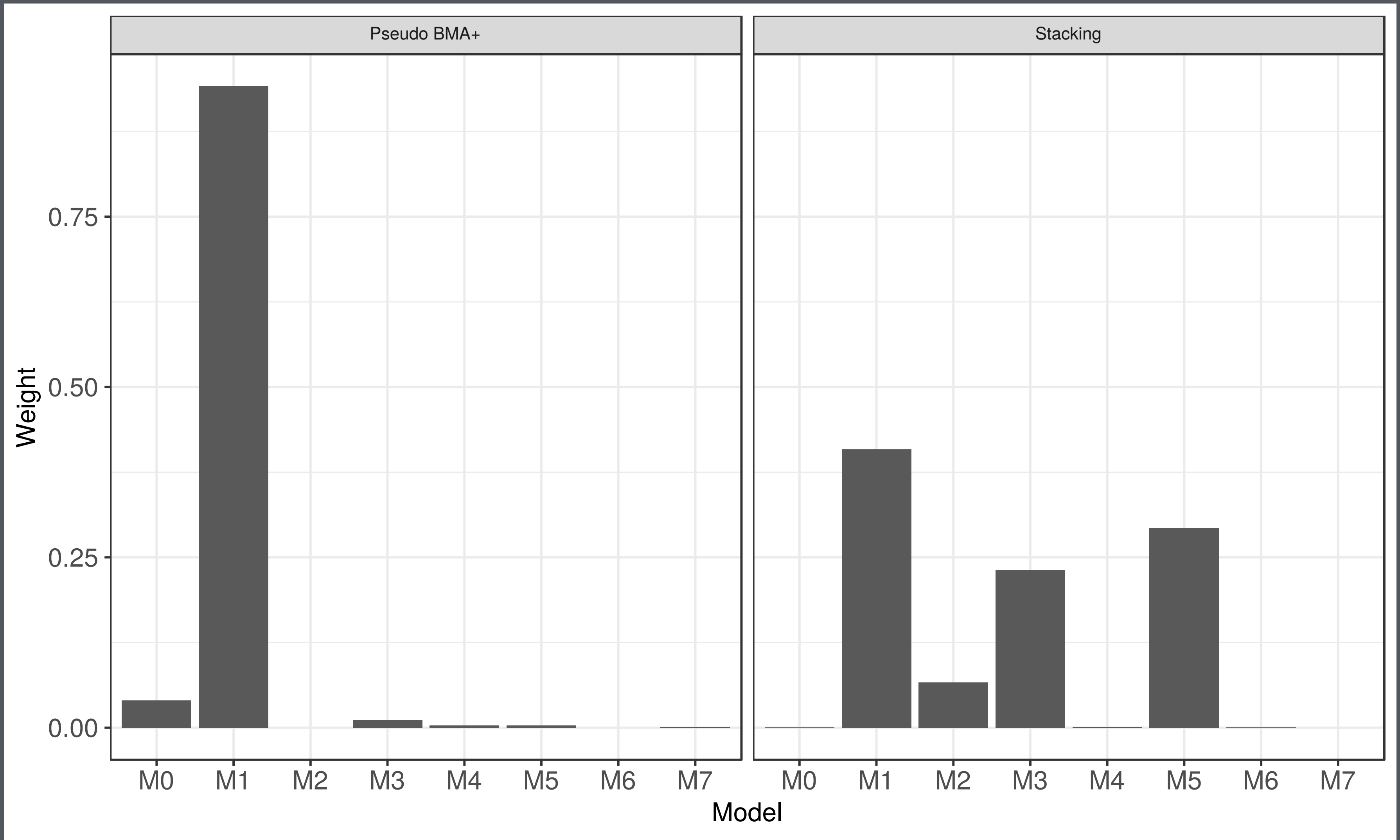
Vehtari, Aki, Andrew Gelman, and Jonah Gabry. "Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC." *Statistics and Computing* 27.5 (2017): 1413-1432.

$$\max_{w}\frac{1}{n}\sum_{i=1}^{n}\log\left(\sum_{k=1}^{K}w_k p(y_i^{OE}\,|\,y^{WT}, M_k)\right) \quad \textbf{subject to} \quad w_k \geq 0,\ \sum_{k=1}^{K}w_k = 1$$

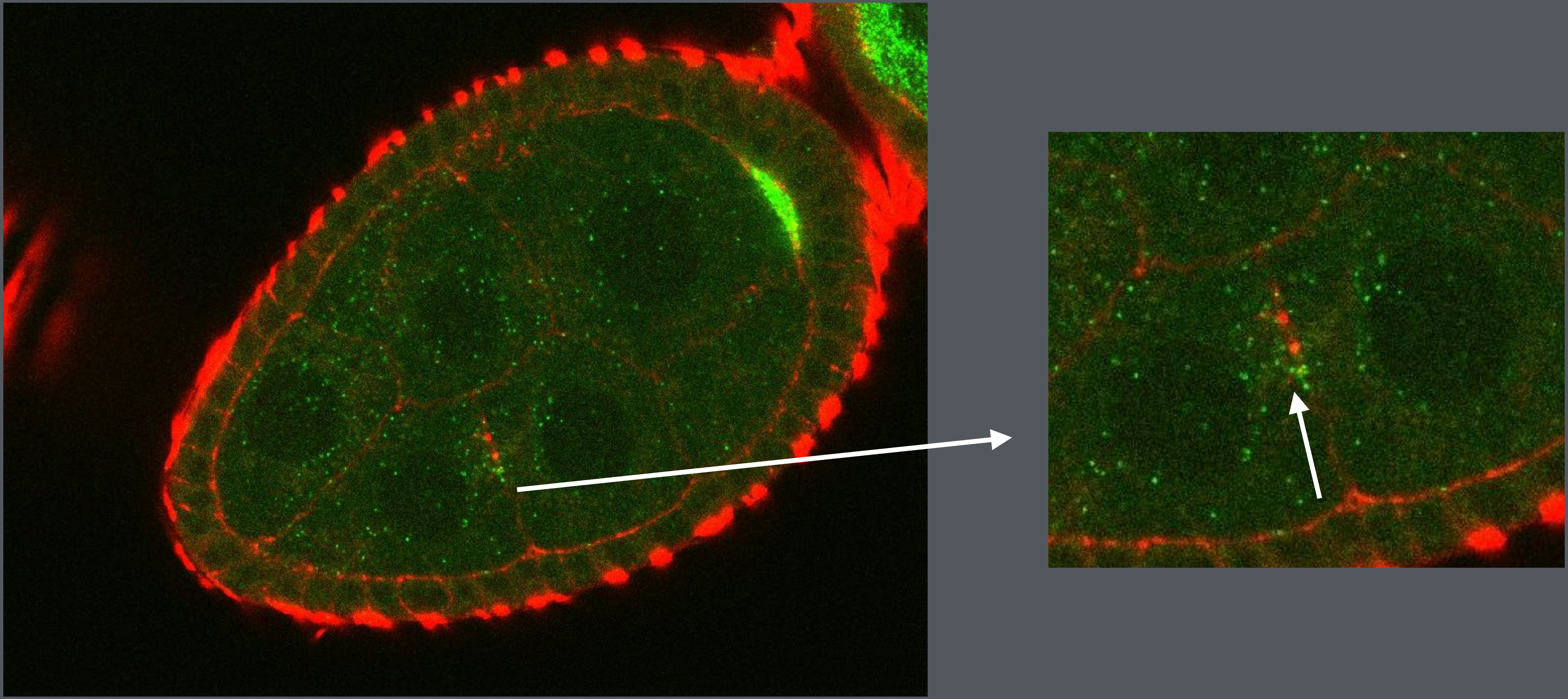
Yao, Yuling, et al. "Using stacking to average Bayesian predictive distributions." *arXiv preprint arXiv:1704.02030*(2017).

Model comparison

	Production	Blocking	Density dependent transport
M0	0	0	0
M1	0	1	0
M2	0	0	1
M3	1	0	0
M4	1	0	1
M5	1	1	0
M6	0	1	1
M7	1	1	1



Why don’t the predictions agree?



Blocking of ring canals

Conclusions

- Simple model connected to data via Bayesian inference is powerful in distinguishing between hypotheses
- Tightly regulated balance between between production and transport
- Crowding of RNA-protein complexes helps to regulate robustness of mRNA localization via blocking of ring canals

Acknowledgements

Ruth E. Baker http://www.iamruthbaker.com/

Richard M. Parton

Ilan Davis

EPSRC
Engineering and Physical Sciences Research Council

Wolfson Centre for Mathematical Biology
wcmb
MATHEMATICAL INSTITUTE

SYS bio

Experimental verification of a coarse-grained model of mRNA localization reveals robustness regulated via crowding

Jonathan U. Harrison, Richard M. Parton,
Ilan Davis, Ruth E. Baker

BIRS, Banff 15th November 2018

@jonty3502

UNIVERSITY OF OXFORD
Mathematical Institute

Oxford Mathematics