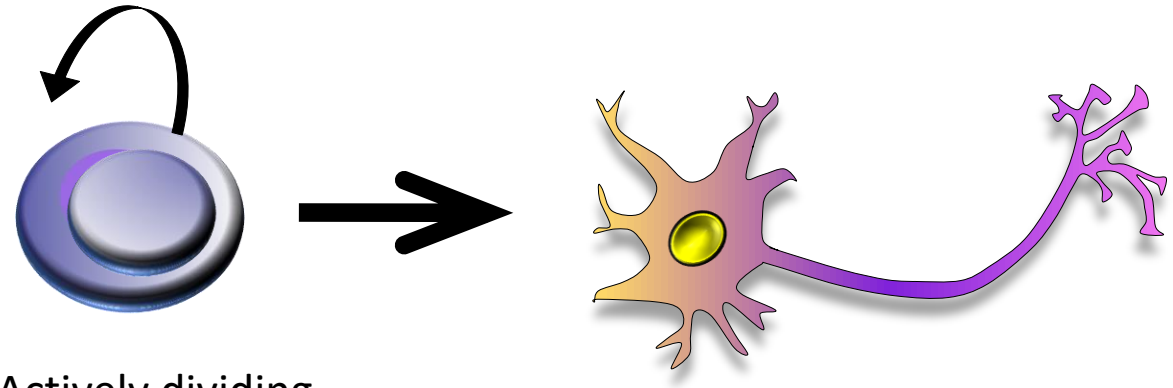
Roles of noise in shaping gene expression dynamics

Jochen Kursawe

Cell state transitions are a key contributor to embryonic development

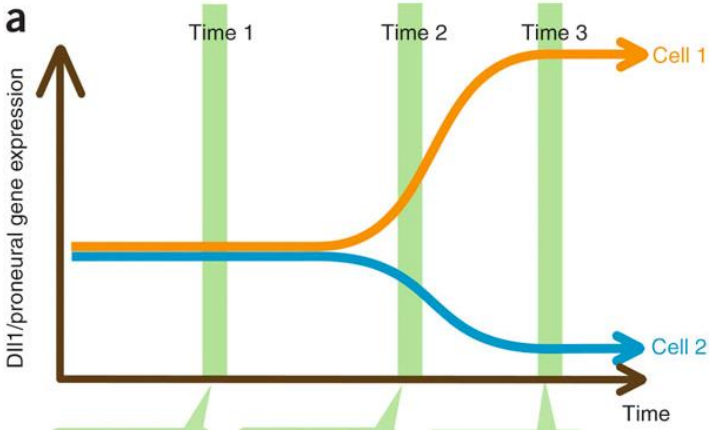


Actively dividing stem/progenitor cell

Neuron

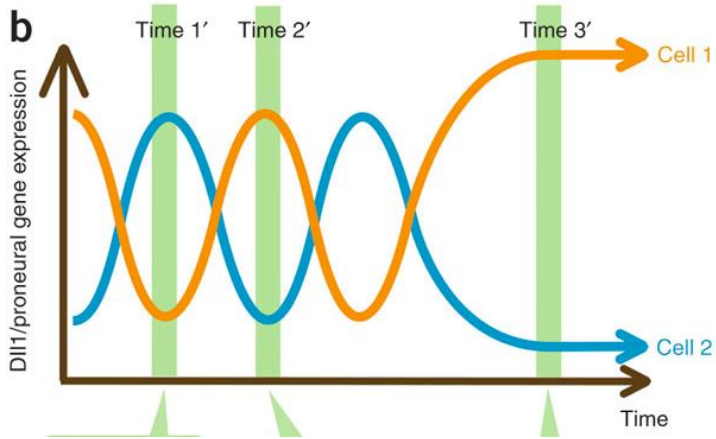
Dynamic changes in gene expression underly novel mechanisms of cell state transitions

Classical view



Genes are upgregulated or downregulated over time as cells change their fate

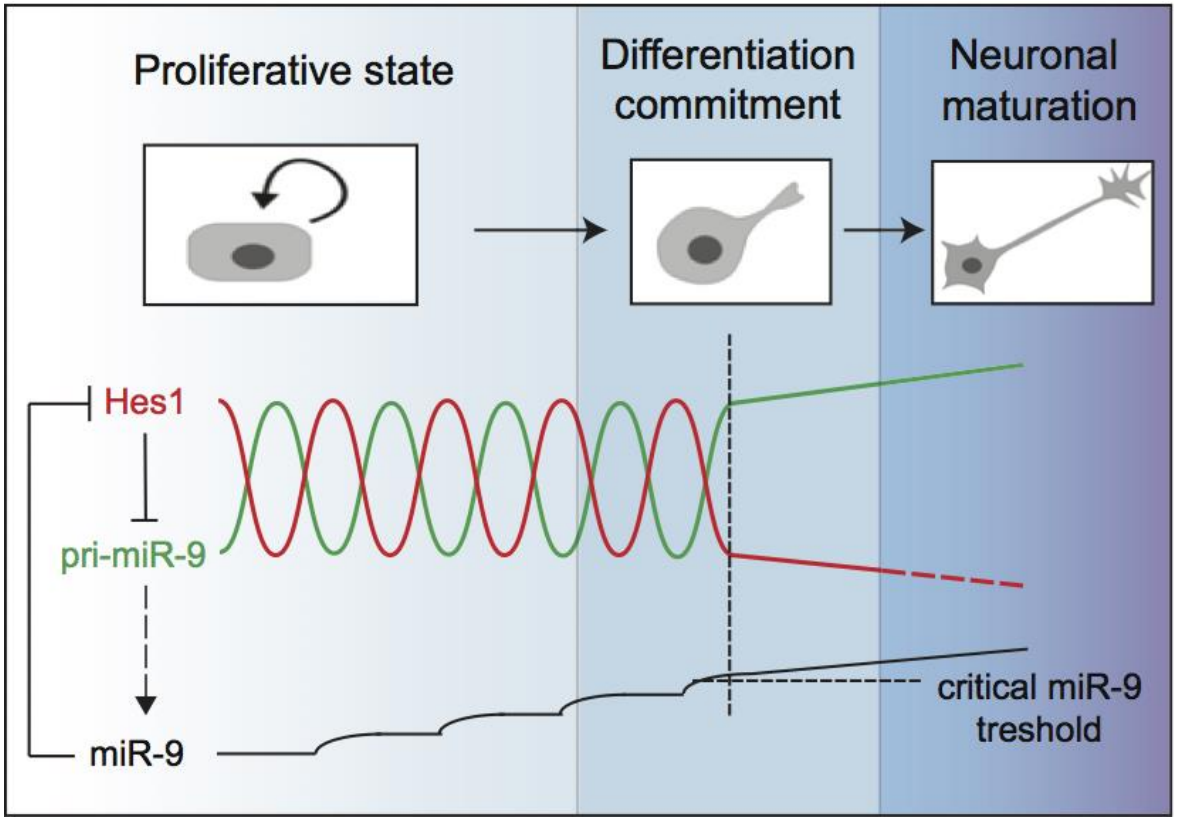
New, dynamic view



Genes oscillate and *change in dynamics* drive transitions

Proposed and reviewed by Kageyama et al *Nature Neuroscience,* 2008

Embryonic neural differentiation is controlled by a gene oscillator acting as a timer

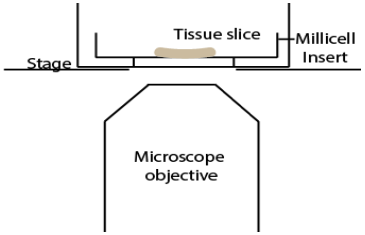


Bonev et al, (2012), Cell Reports
Goodfellow et al., (2014) Nature Comm
Phillips et al., (2017) eLIFE

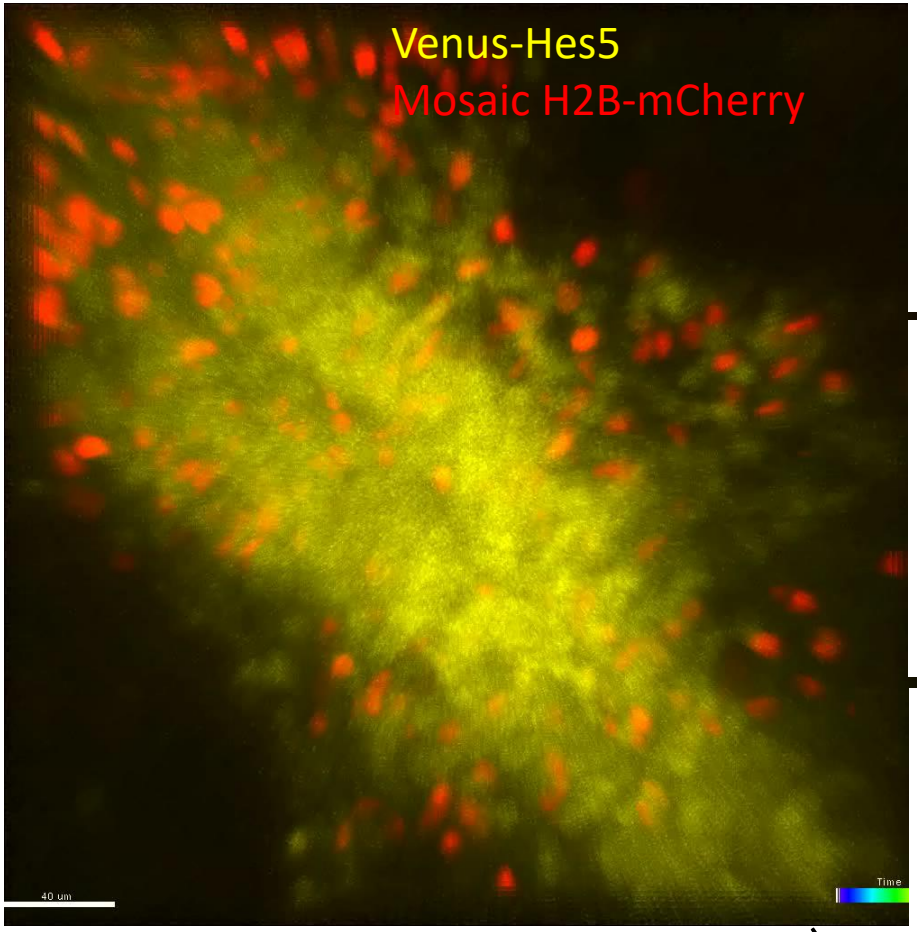
Live imaging of Hes5 dynamics in spinal cord neural progenitors enables analysis of oscillations in a tissue context

Cerys Manning

Dissect live embryos and slice using vibratome

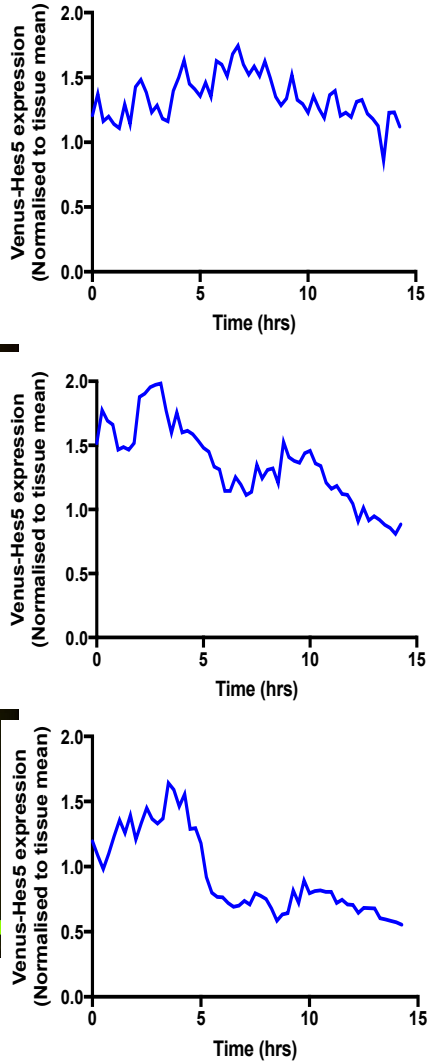


Dorsal



Ventral

Hes5 dynamics

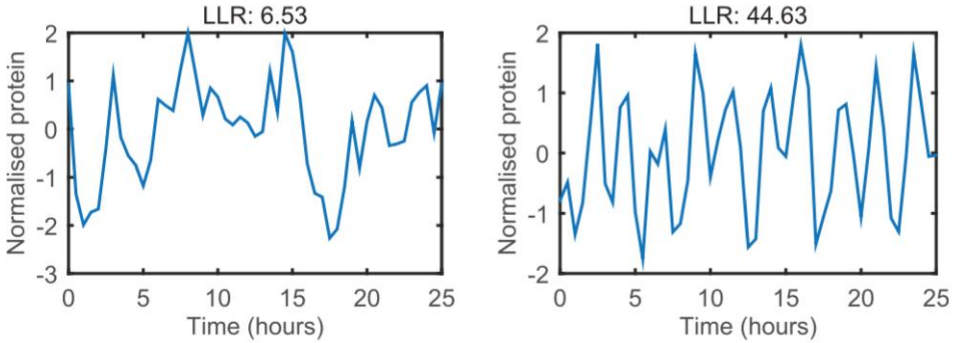


E10 Mouse Spinal cord live section of Venus-Hes5$^{+/-}$ Sox1CreERT2$^{+/-}$ R26R H2BmCherry loxP$^{+/-}$
2.5 mg of Tamoxifen administered I.P to pregnant female 18hrs before dissection

Identification of oscillatory dynamics requires statistical analysis

Tool to analyse periodicity in noisy data using Gaussian Processes. *Phillips et al., 2017 Plos Com Biol*

Traces of gene expression



Veronica Biga

Model fitting

$$K_{OU}(\tau) = \tilde{\sigma}_{OU} \exp(-\alpha\tau)$$ Aperiodic fluctuations

$$K_{OUosc}(\tau) = \tilde{\sigma}_{OUosc} \exp(-\alpha\tau)\cos(\beta\tau)$$ Oscillations

Signal SD

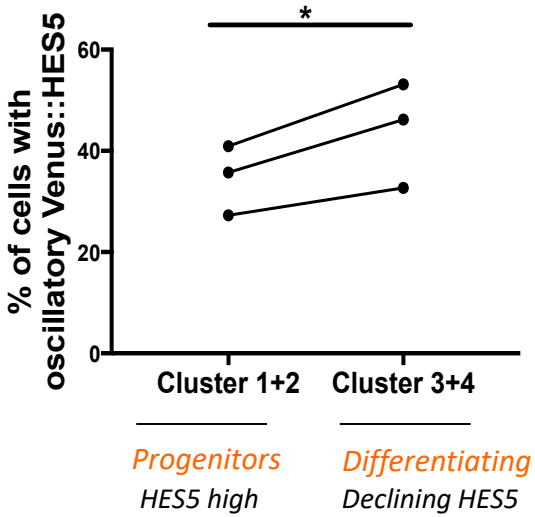
Periodicity of frequency β

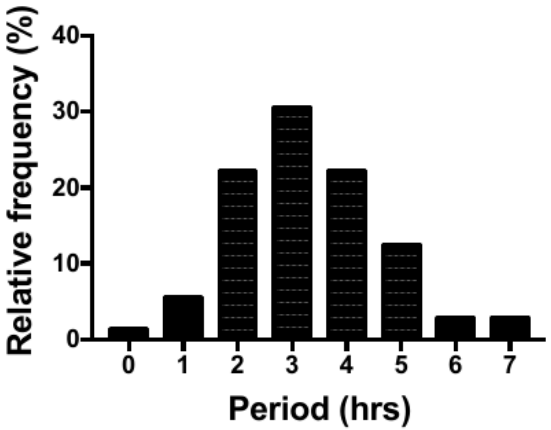
Model selection by Log likelihood Ratio (LLR)

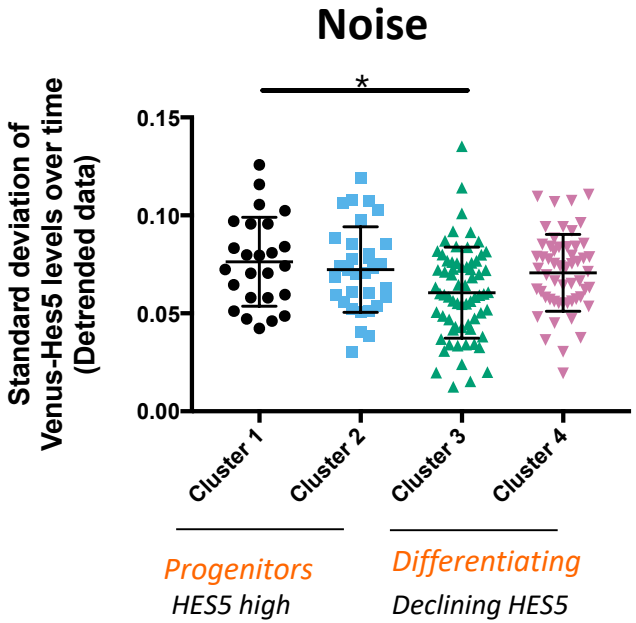
$$LLR = LL_{OUosc} - LL_{OU}$$

Which cell states show oscillatory HES5 dynamics?

Oscillations are more frequent in differentiating cells; dividing progenitors are noisy

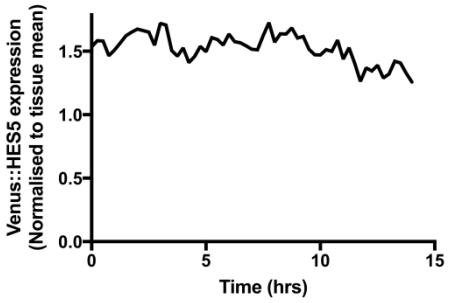




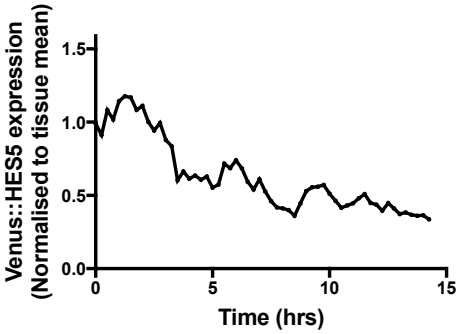


Oscillations may originate from noisy expression

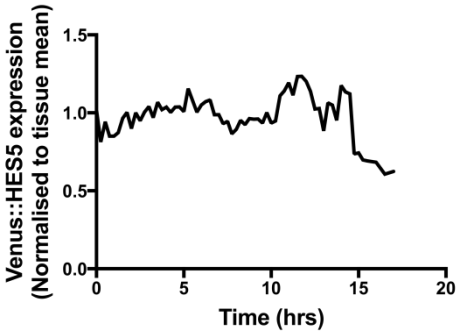
Aperiodic but noisy



"Oscillatory-while-declining" example



Converting



Key modelling questions:

- Do we understand the mechanisms governing Hes5 gene expression oscillations?
- Can we understand the stochasticity of this system?
- Can we identify mechanisms that can explain transitions from aperiodic to oscillatory gene expression?
- What predictions can we make from this?

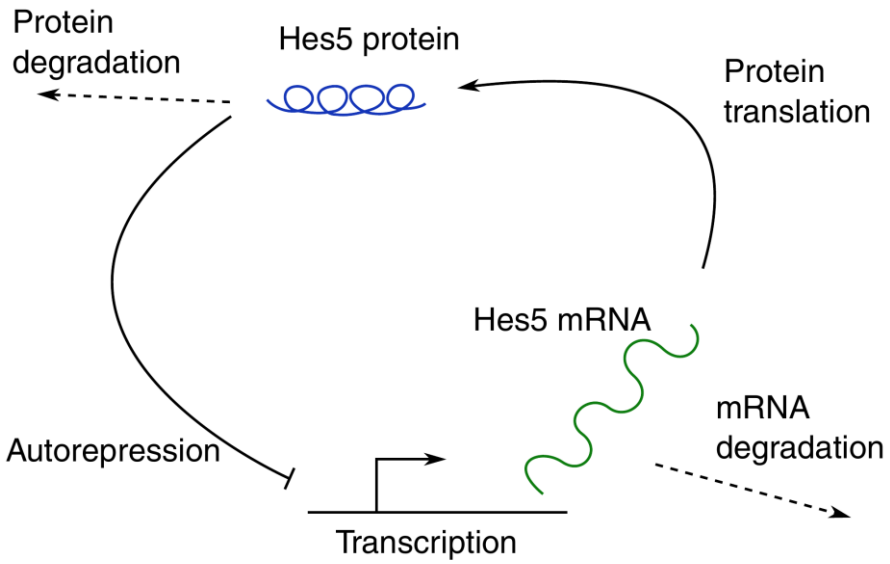
Step one: apply a mathematical model of transcriptional autorepression

Rate of change | Production | Degradation | Noise

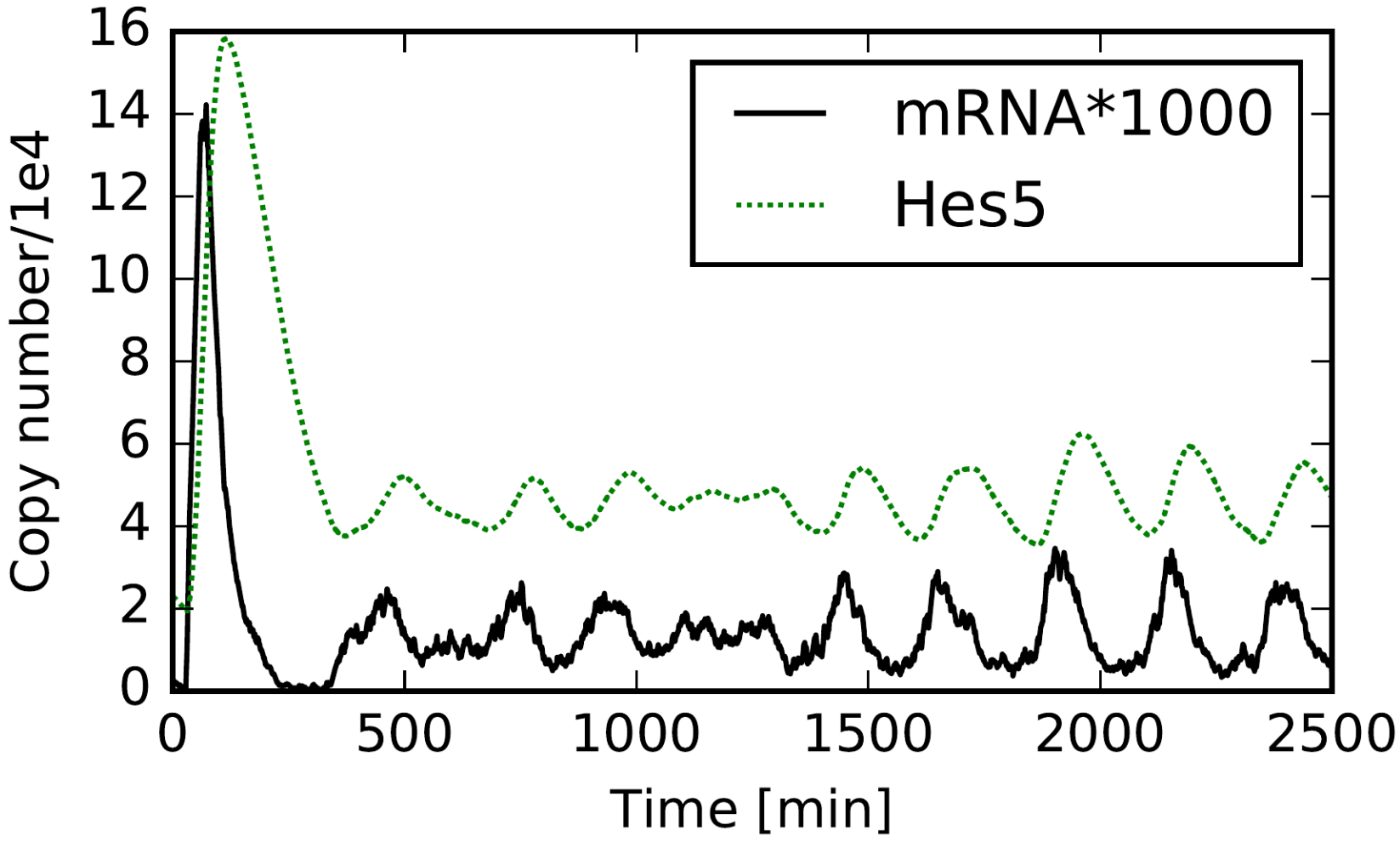
$$\begin{aligned} \frac{dM}{dt} &= \alpha_m G(P(t-\tau)) - \mu_m M(t) + \sqrt{\mu_m M(t) + \alpha_m G(P(t-\tau))}\,\xi_m(t) \\ \frac{dP}{dt} &= \alpha_p M(t) - \mu_p P(t) + \sqrt{\mu_p P(t) + \alpha_p M(t)}\,\xi_p(t) \end{aligned}$$

$$G(P(t-\tau)) = \frac{1}{1 + (P(t-\tau)/P_0)^n}$$

[1] N. A. Monk. Curr. Biol. 13(16), 1409–1413. (2003)
[2] T. Brett, T. Galla. J. Chem. Phys. 140(12), 124112. (2014)

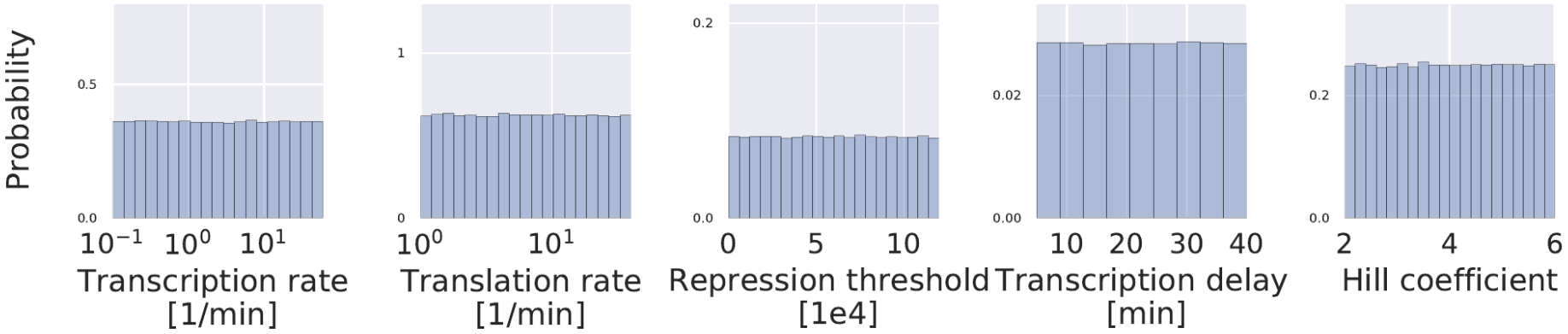


The model generates time traces of Hes5 protein and mRNA expression

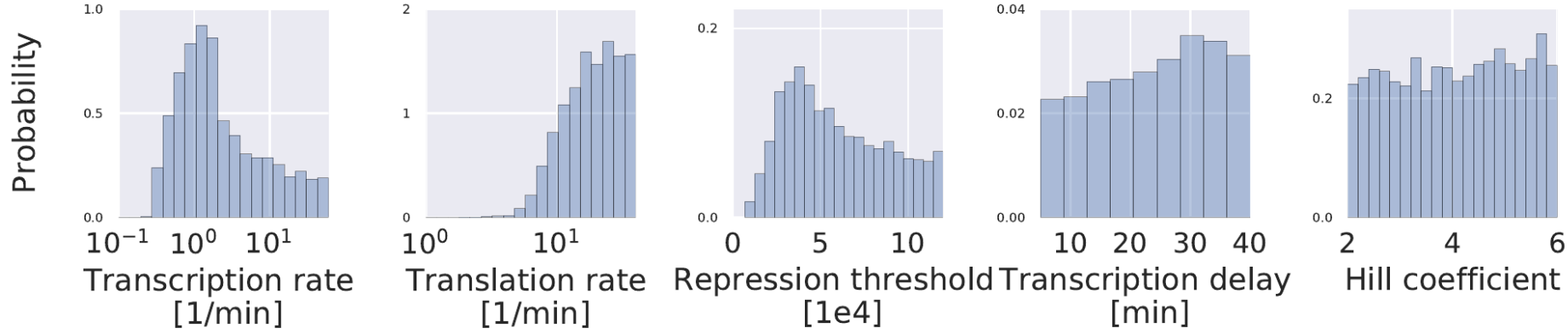


Step two: apply Bayesian inference to parameterise the model

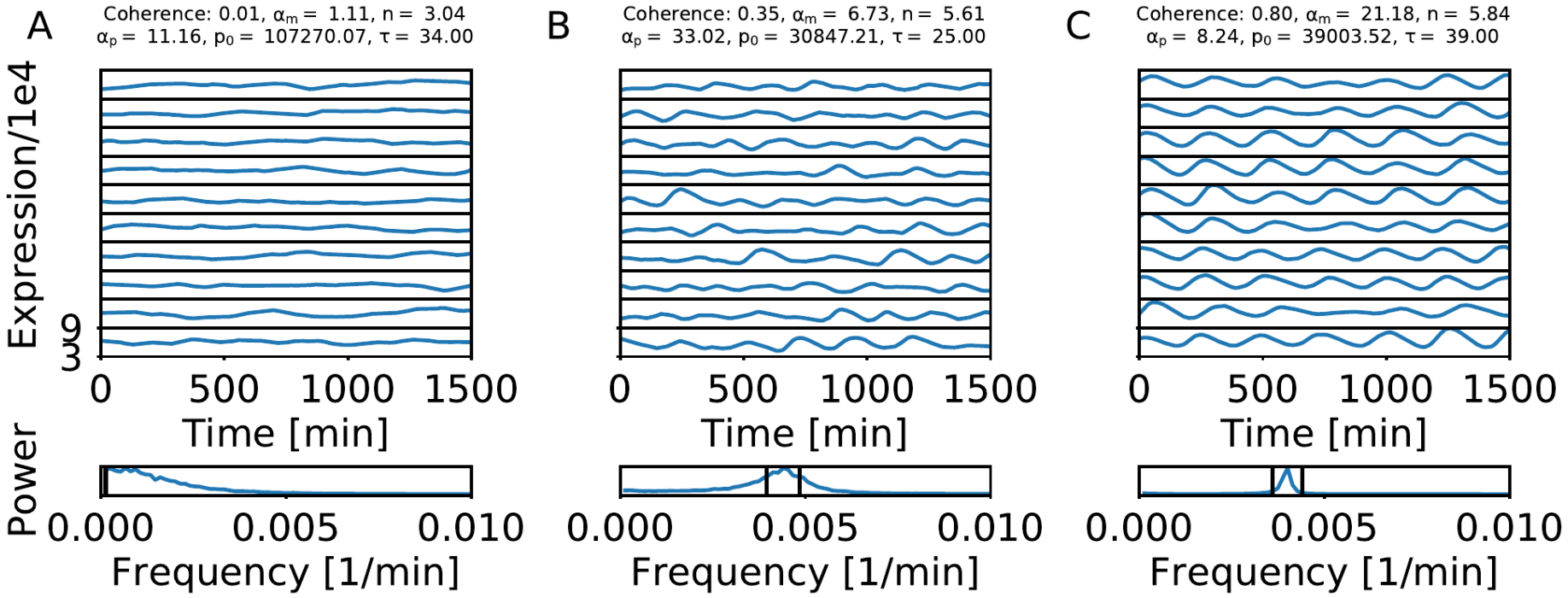
Prior probability p(θ)



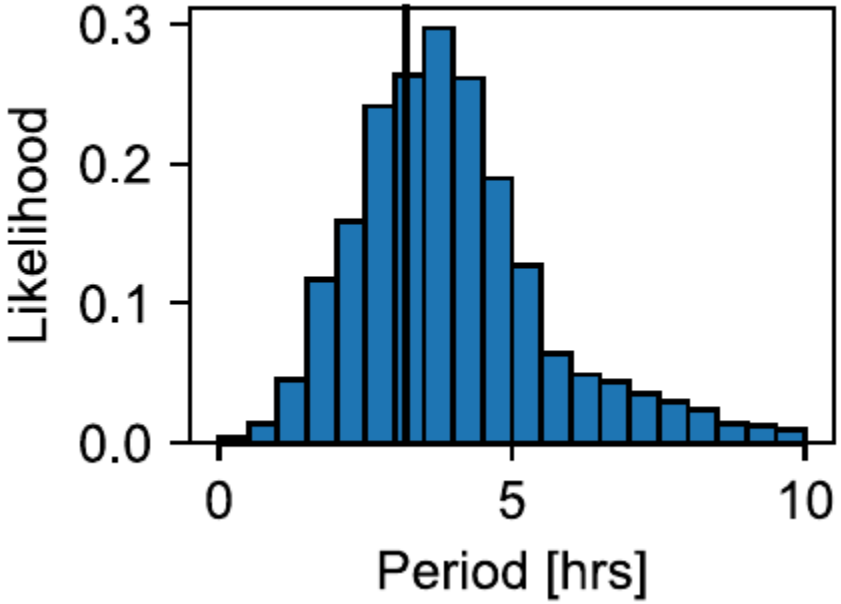
Posterior probability p(θ|D) ∝ p(D|θ)p(θ), Summary statistics: mean and standard deviation of Hes5 expression

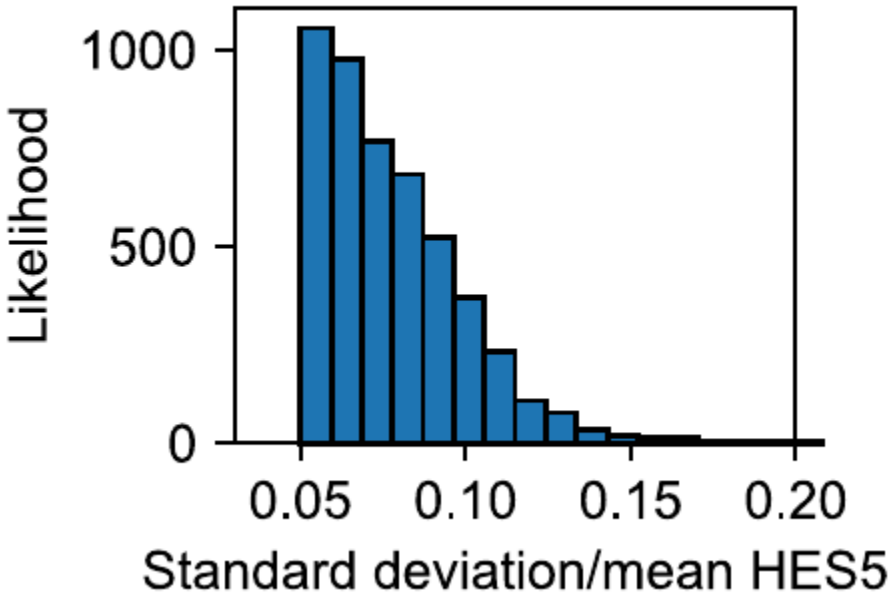


Modelled traces of gene expression can exhibit aperiodic and oscillatory dynamics

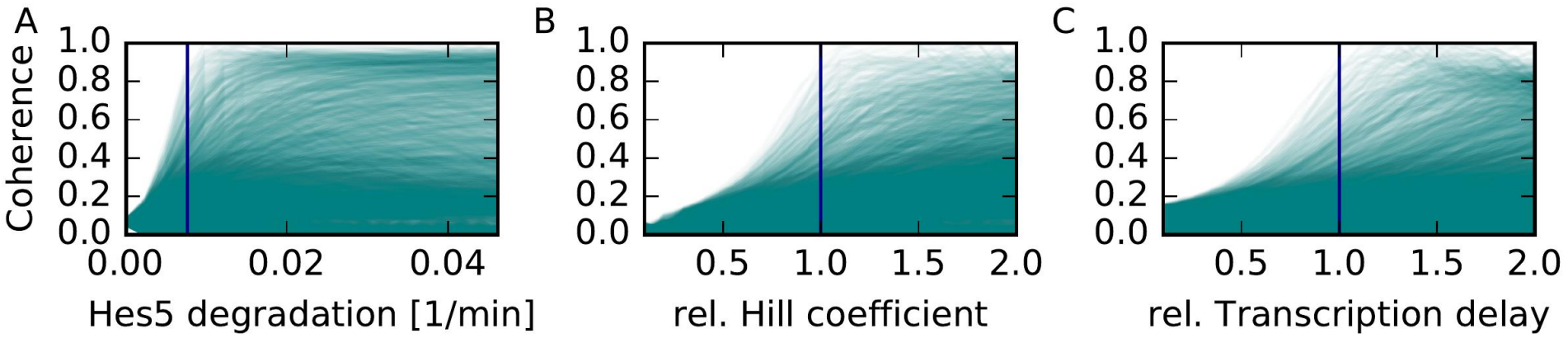


The model correctly predicts the period and amplitude of the oscillations

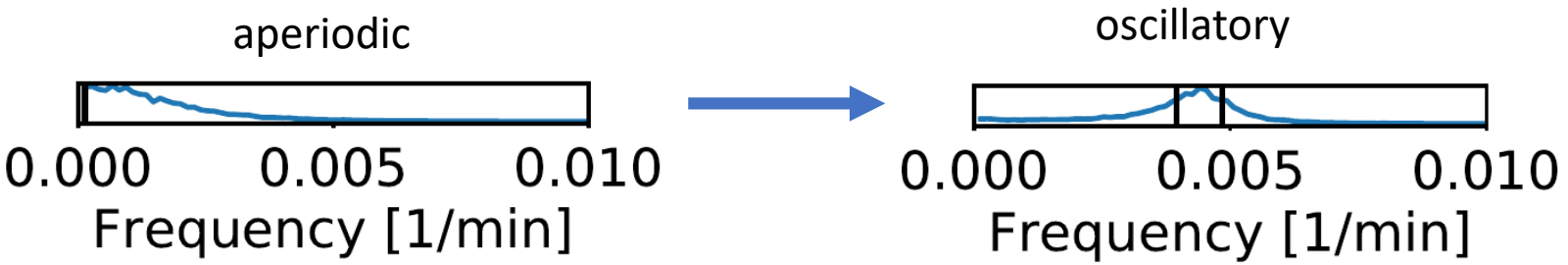


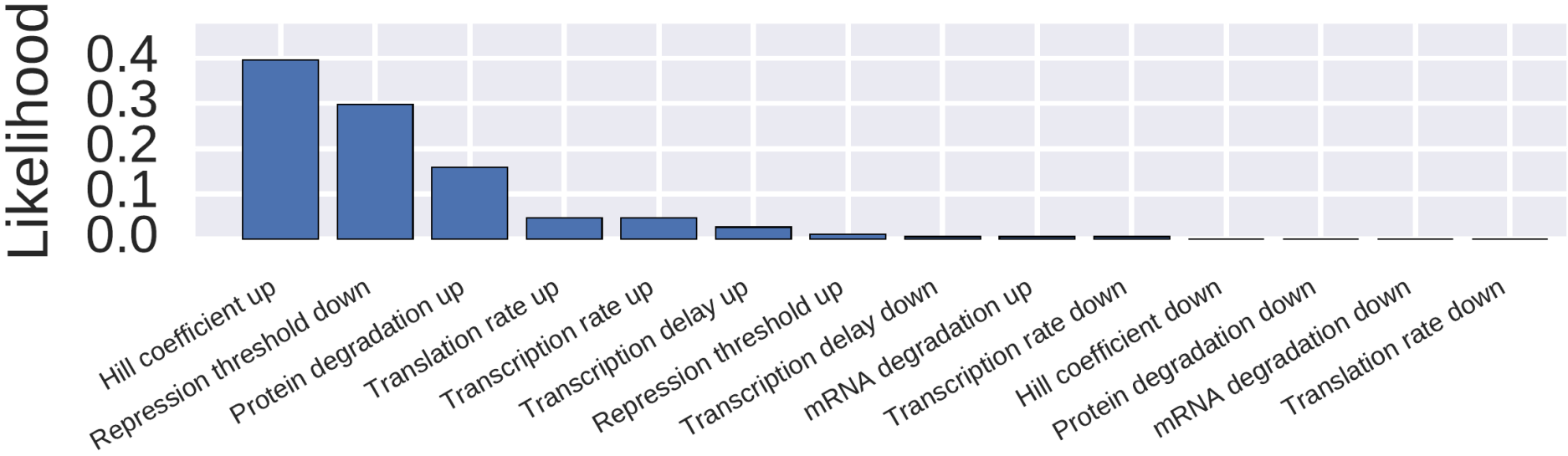


The model is poised at the bifurcation point between aperiodic and oscillatory dynamics

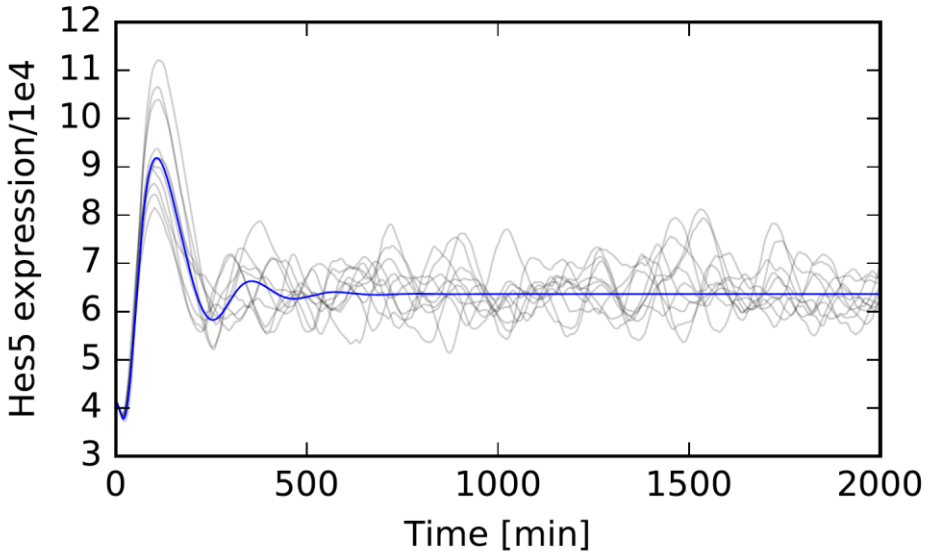


Transitions from aperiodic to oscillatory gene expression can be initiated by changes in individual model parameters

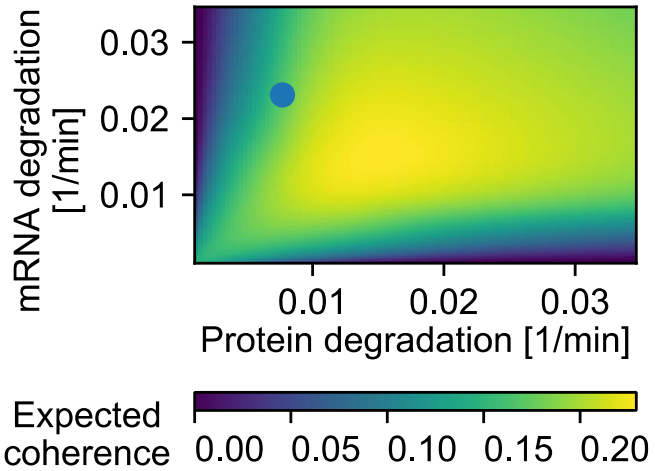




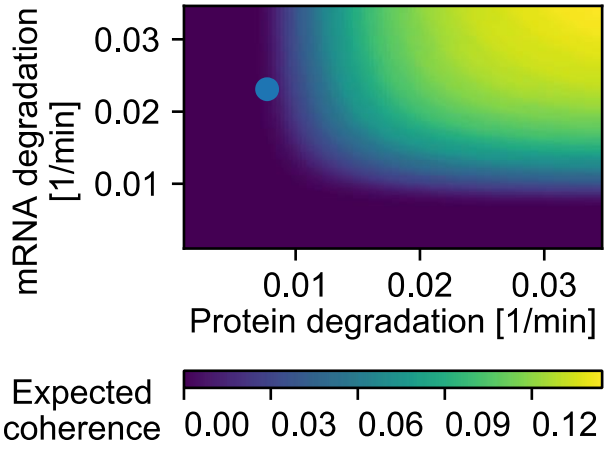
Oscillations are an example of stochastic amplification



Stochastic model



.. vs deterministic model

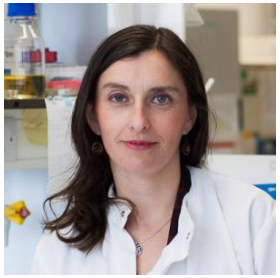


Manning, C. S., Biga, V., Boyd, J., Kursawe, J., Ymisson, B., Spiller, D. G., … Papalopulu, N. (2018). bioRxiv, DOI: 10.1101/373407

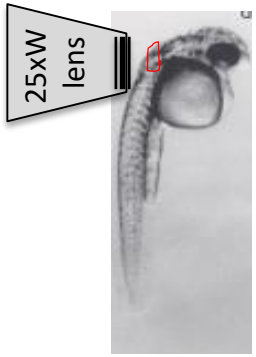
Conclusions

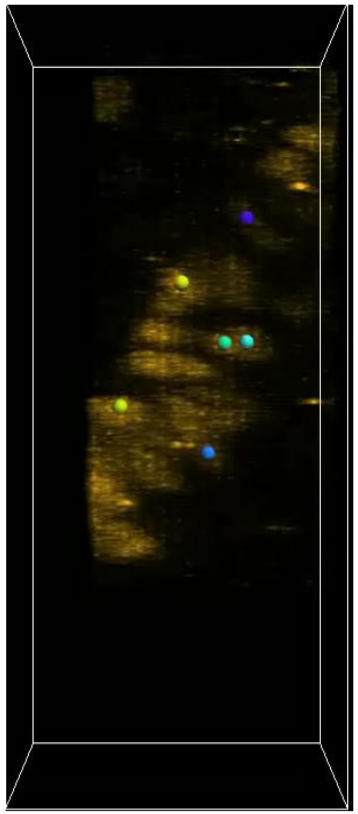
- Hes5 oscillations in spinal cord neural progenitor cells can be described by a model of transcriptional autorepression with delay
- The model can be used to make experimentally testable predictions
- Bayesian model interpretation enables the systematic evaluation of uncertainty for model parameters and predictions

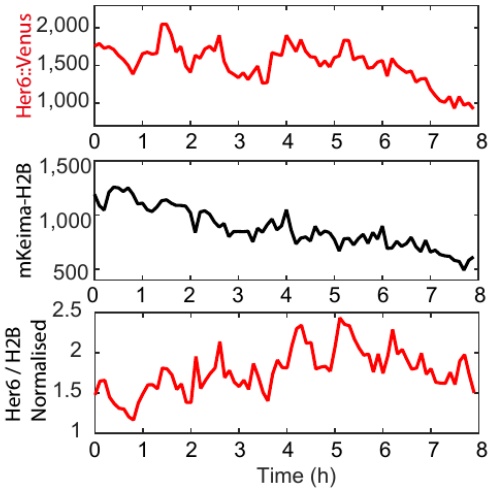
New zebrafish line enables observation of oscillations in vivo

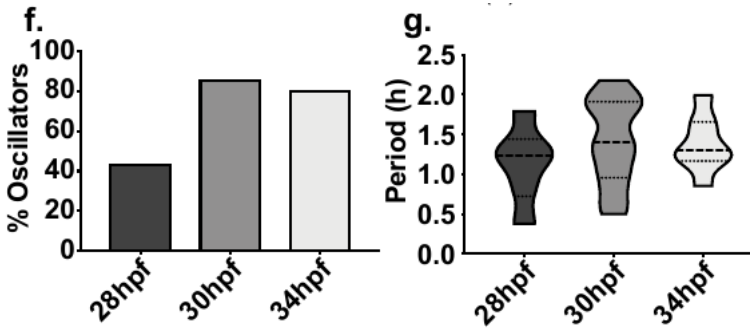


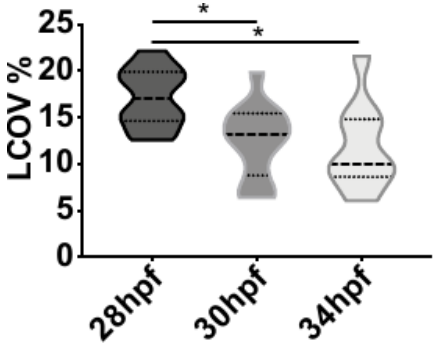
Ximena Soto









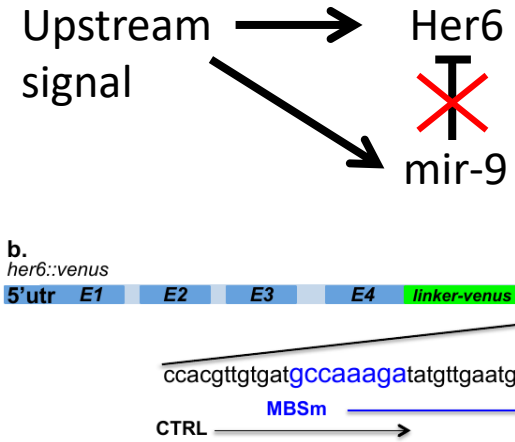


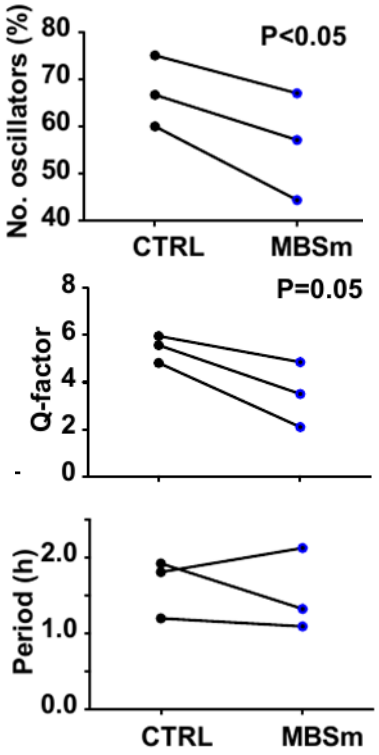
New biorxiv preprint

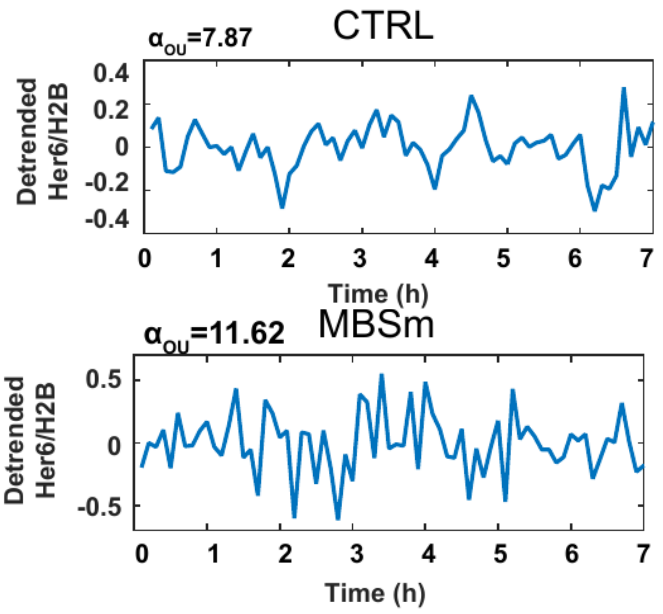
Soto et al., **miR-9 mediated noise optimization of the her6 oscillator is needed for cell state progression in the Zebrafish hindbrain**

https://www.biorxiv.org/content/10.1101/608604v1

Perturbing microRNA binding enables perturbation of oscillations





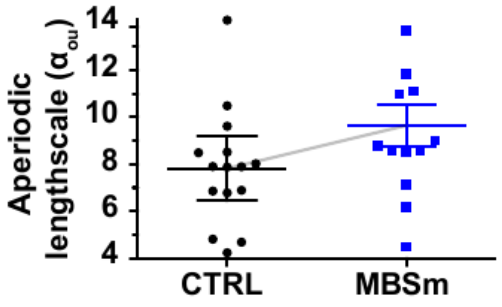


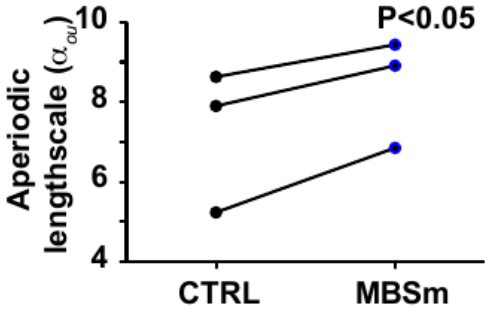
Covariance **Stochastic**

$$K_{OU}(\tau) = \sigma \exp(-\alpha_{OU}\tau)$$

Parameters: *Signal variance*, *Aperiodic lengthscale*

τ=|t-t'| represents time interval





Questions for a mathematical model

- Do we understand the emergence of the observed oscillations, and changes in dynamics under the MBS experiment?
  - Are the observed changes in dynamics upon CTRL->MBS perturbation consistent with simply changing mRNA translation and degradation?
- How does noise in emerge in the Her6 oscillator? How does the noise get regulated micro-RNA?

We modify the mathematical model to account for transcriptional noise

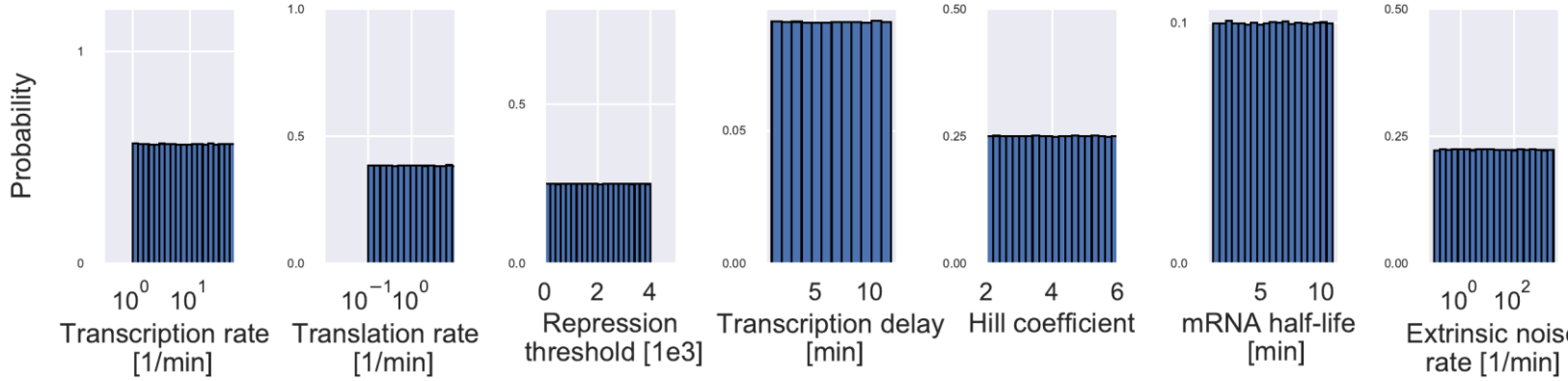
$$\frac{dM}{dt} = -\mu_m M(t) + \alpha_m G(P(t-\tau)) + \sqrt{\mu_m M(t) + \alpha_m G(P(t-\tau)) + \sigma}\,\xi_m(t),$$
$$\frac{dP}{dt} = -\mu_p P(t) + \alpha_p M(t) + \sqrt{\mu_p P(t) + \alpha_p M(t)}\,\xi_p(t).$$

$$G(P(t-\tau)) = \frac{1}{1 + (P(t-\tau)/P_0)^n}$$

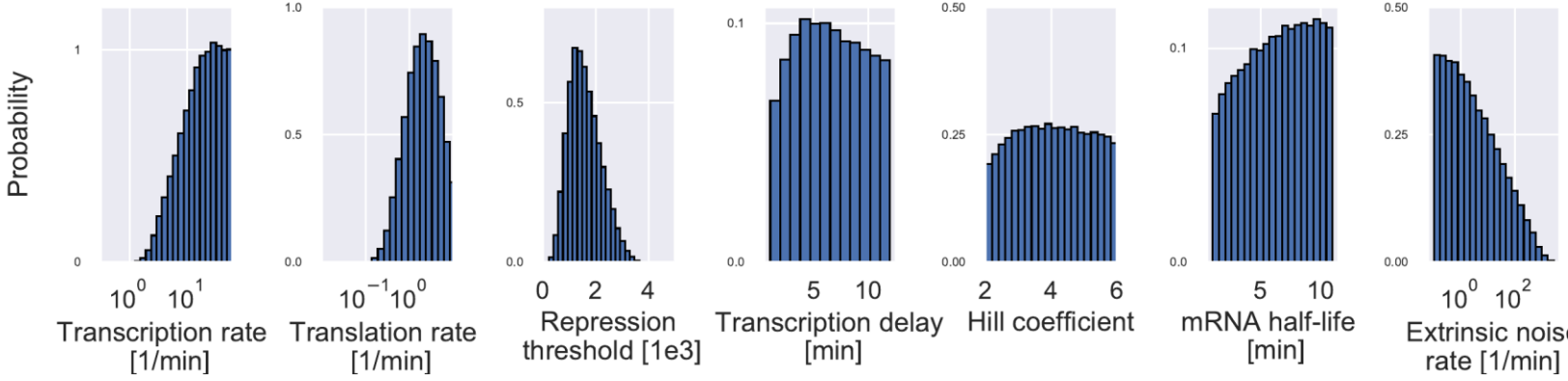
- The new term, σ, accounts for transcriptional noise due to bursting or upstream signal fluctuations

Inference on wildtype oscillations again reveals high parameter uncertainty

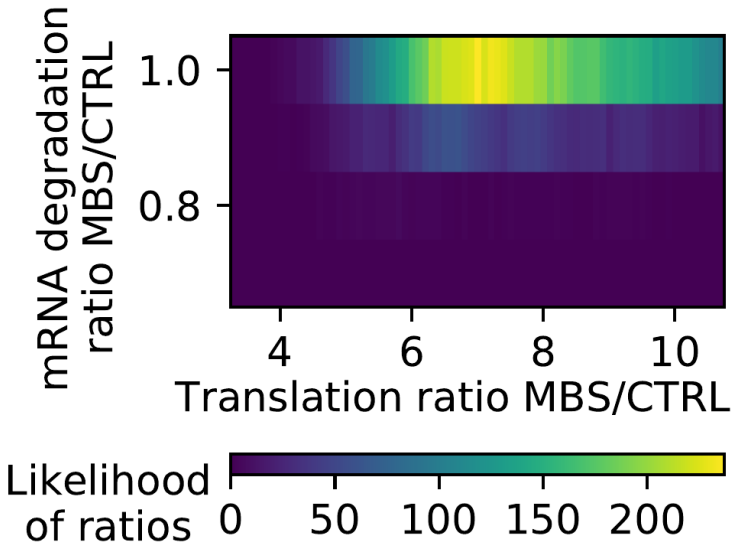
Ximena measured a protein half-life of 11 minutes. For the other parameters, we need to make prior assumptions



Knowing that there are 1000-2500 protein molecules per cell, the signal COV is 5-15%, and we see high-quality oscillations with periods below 150 minutes, we obtain posterior distributions



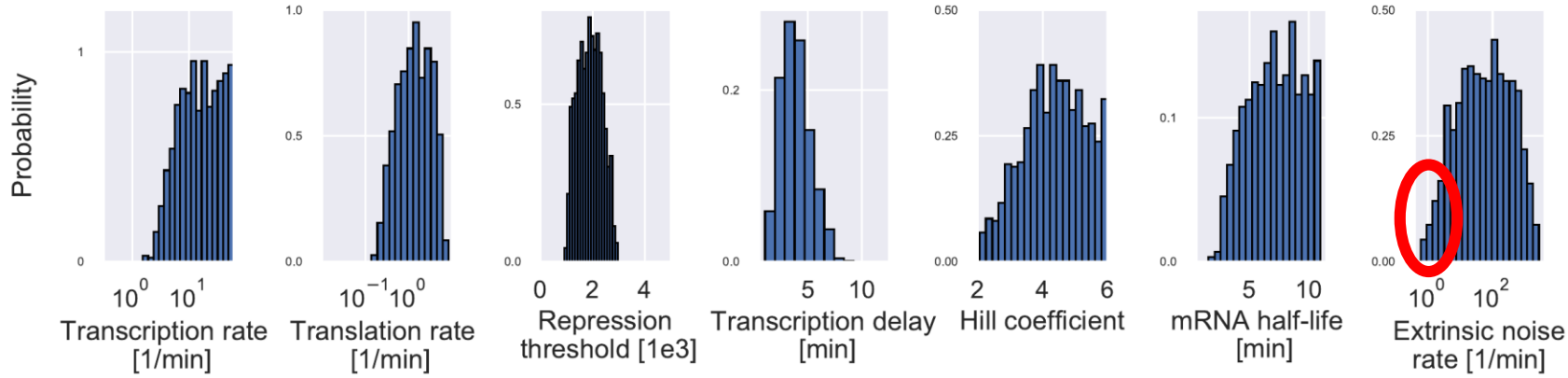
Joint inference on wild-type oscillations and perturbation reduces parameter uncertainty



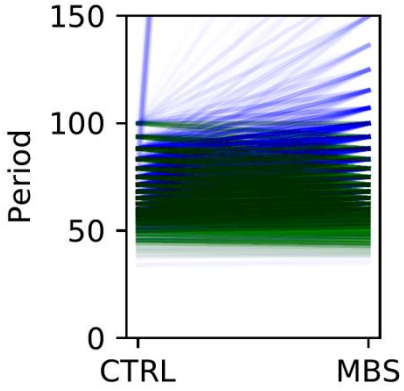
Joint fitting conditions:

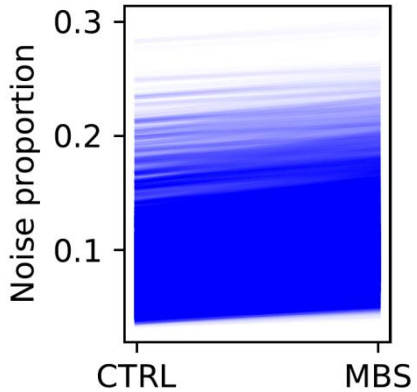
- CTRL oscillations as before
- MBS translation rate and mRNA degradation rate are changed from CTRL oscillations by unknown amounts
- MBS levels are between 1.8 and 2.2 times CTRL levels
- MBS oscillation coherence is lower than CTRL
- Aperiodic lengthscale in MBS is higher than control by >10%

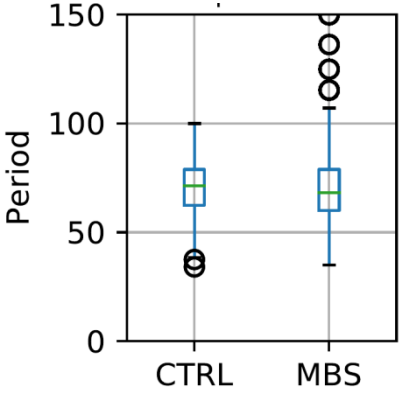
CTRL scenario posterior distributions:

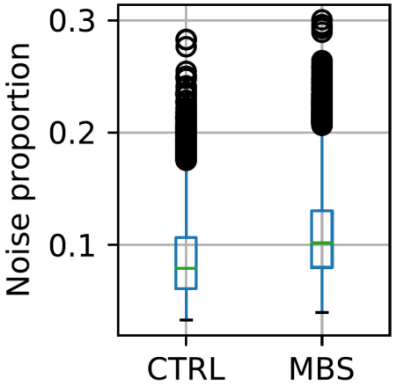


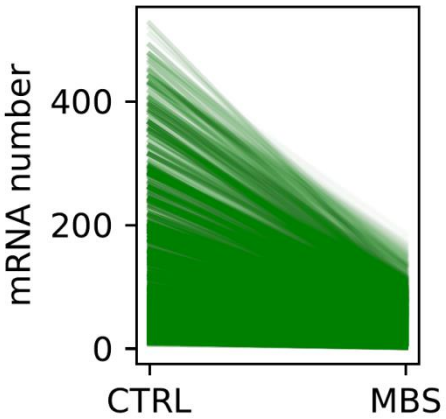
Bayesian posterior predictions inform new experiments

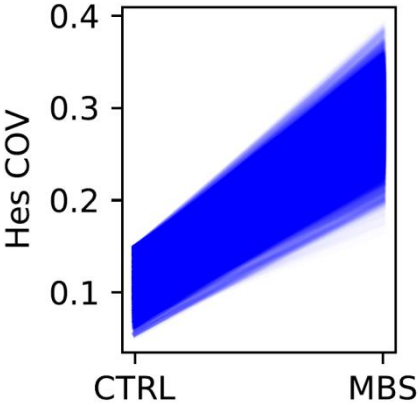


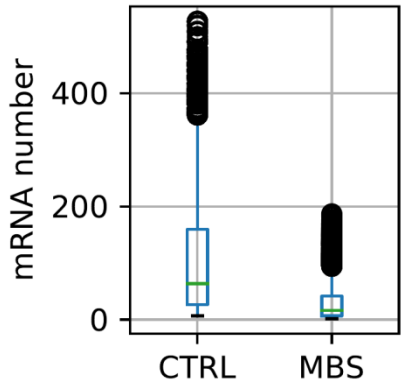


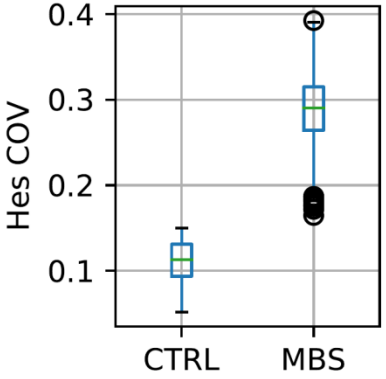


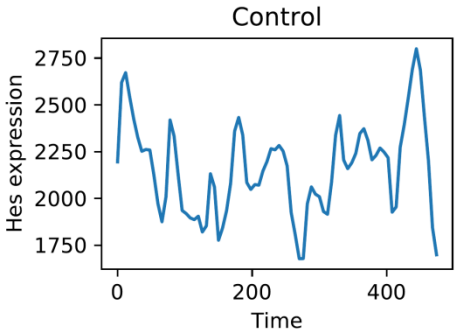


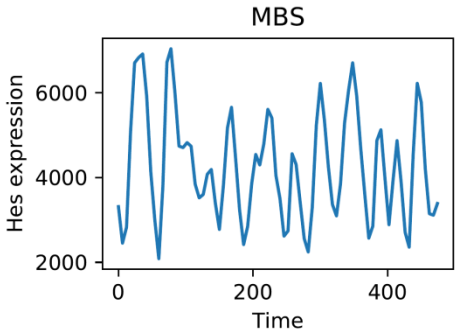












Summary

- Mir9 counteracts detrimental effects of transcriptional noise to enable coherent oscillations
- Mir9 achieves this by reducing the Her6 translation rate
- The model makes multiple experimentally testable predictions:
  - Translation rate increases from CTRL->MBS by a factor >=5
  - The mRNA degradation rate is similar between CTRL and MBS mutant
  - We expect the measured mRNA number in the MBS mutant to be smaller than in CTRL, despite the increase in absolute Her6 levels

Acknowledgements

Papalopulu lab

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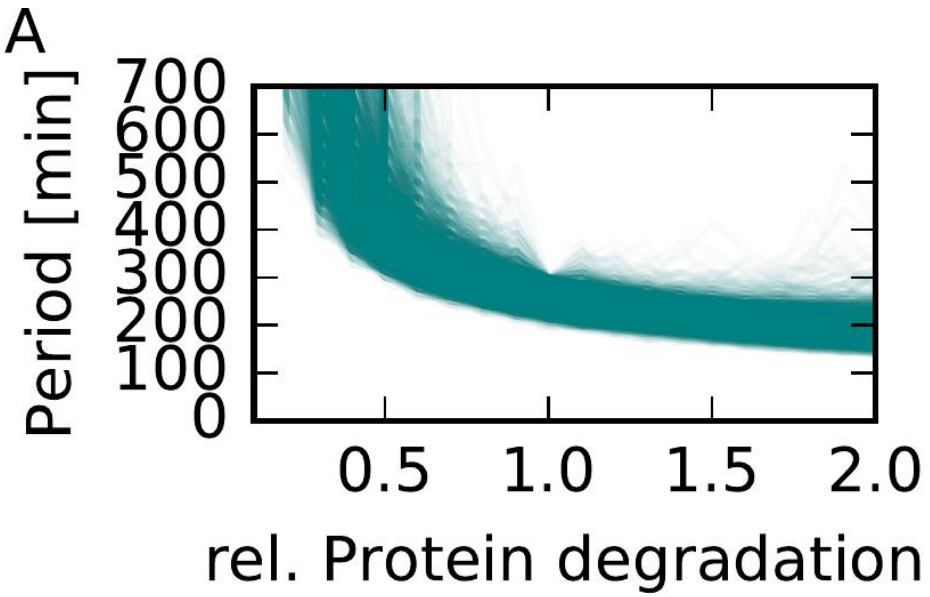
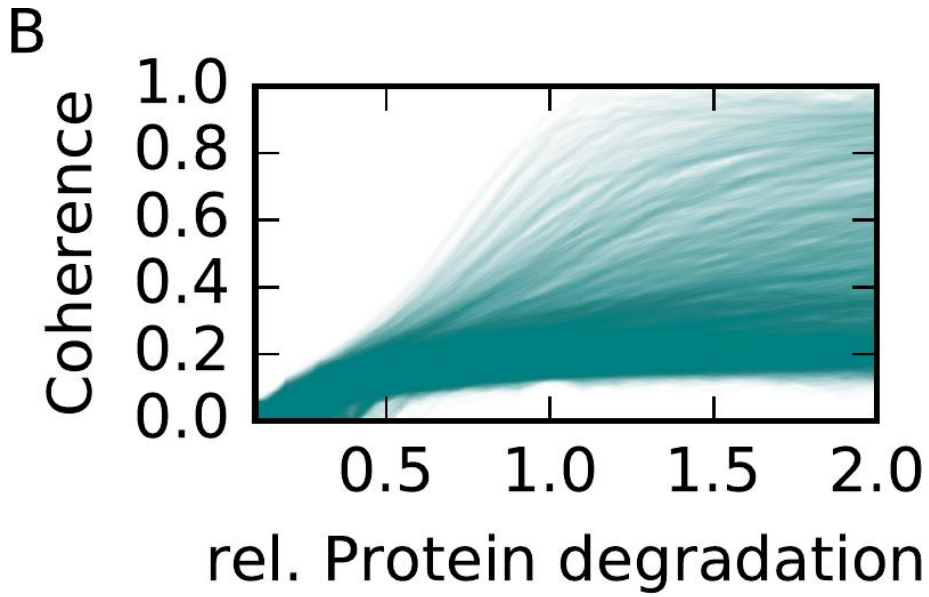
Nitin Sabherwal
Parnian Doostdar
Nancy Papalopulu

wellcome

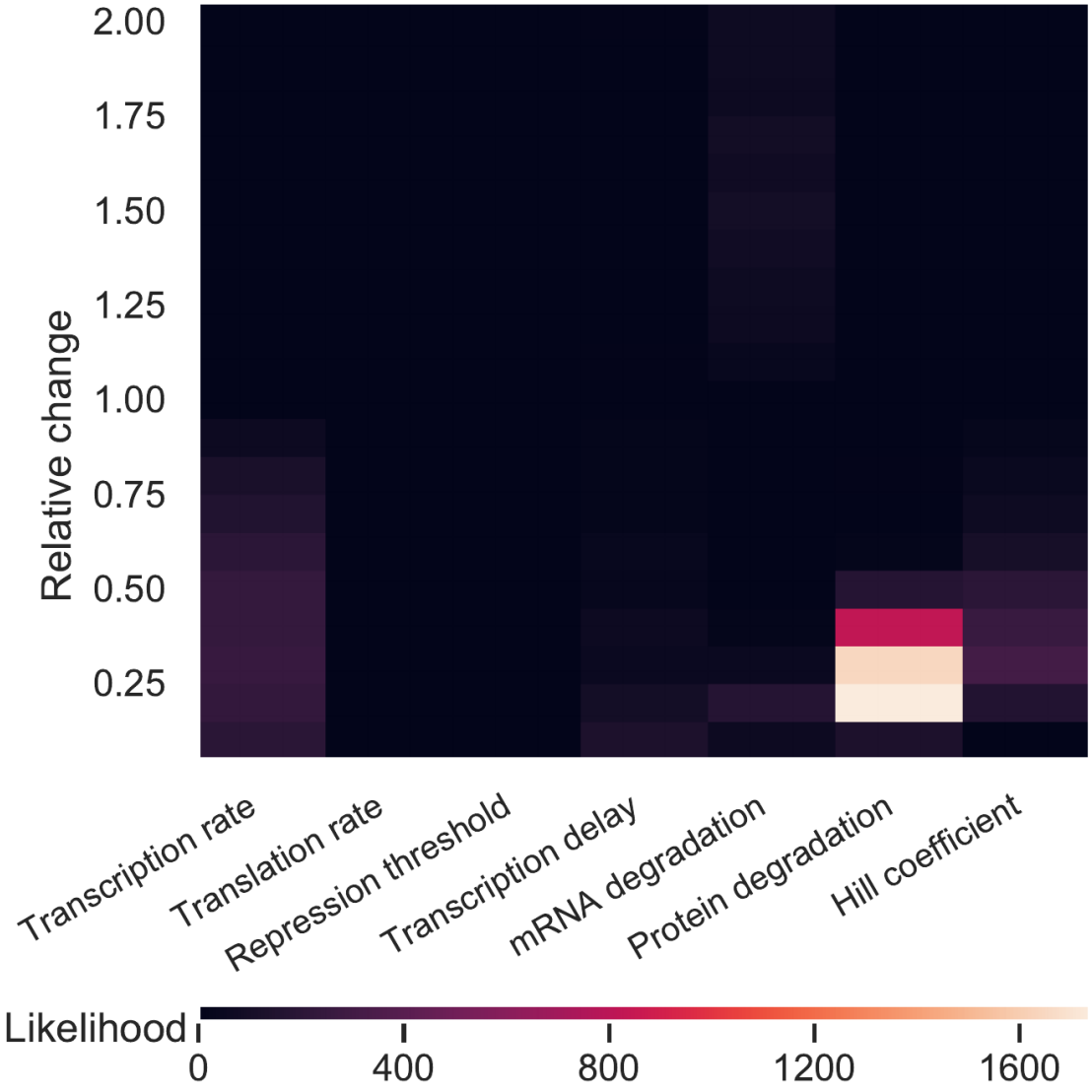
The model predicts that oscillation period can be controlled through changes in the protein degradation rate



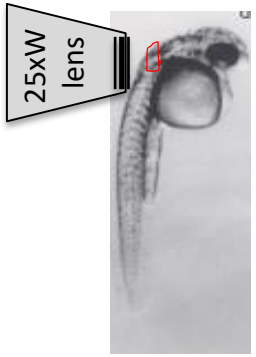


Mathematical modelling is becoming key contributor to experimental design

- Example: which parameter changes can explain differences in gene expression dynamics upon changing cell state?
- Math modelling helps us decide which experiment to do next.

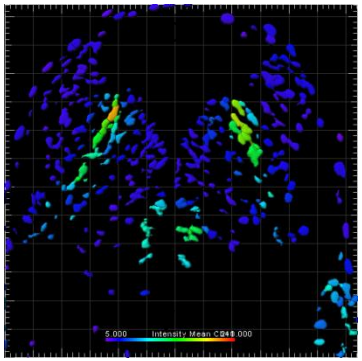


Her6 single cell dynamic expression

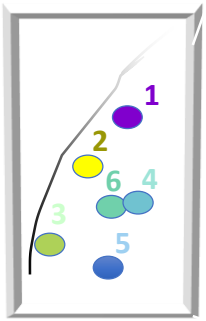


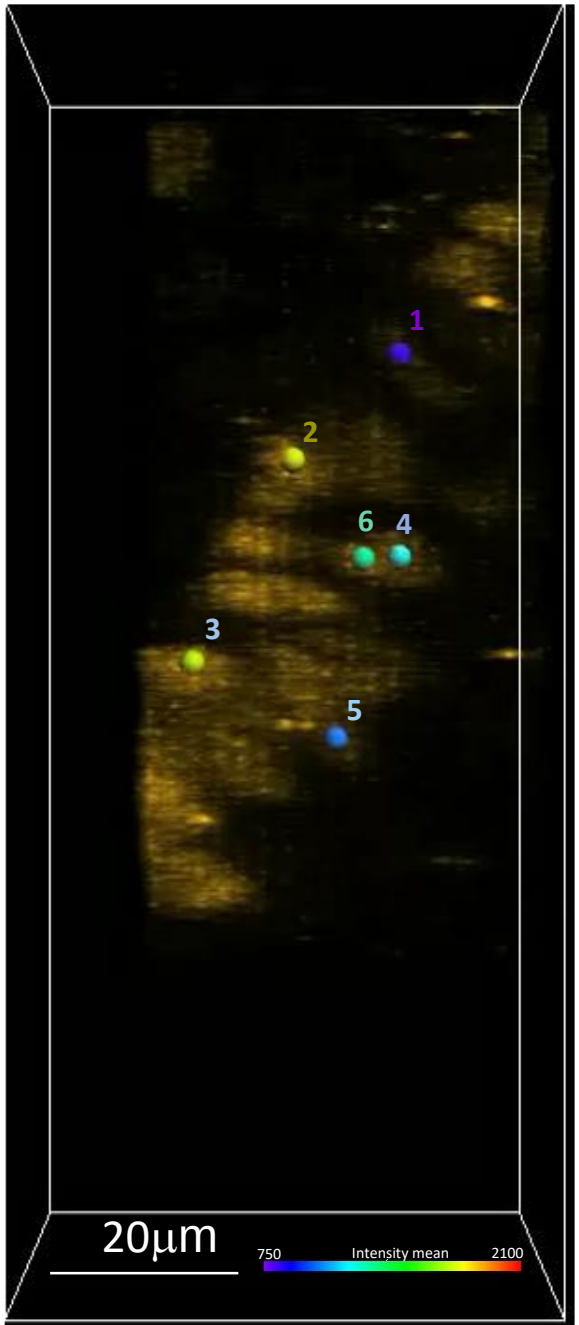
34hpf
8h movie
Every 6min
Z=16

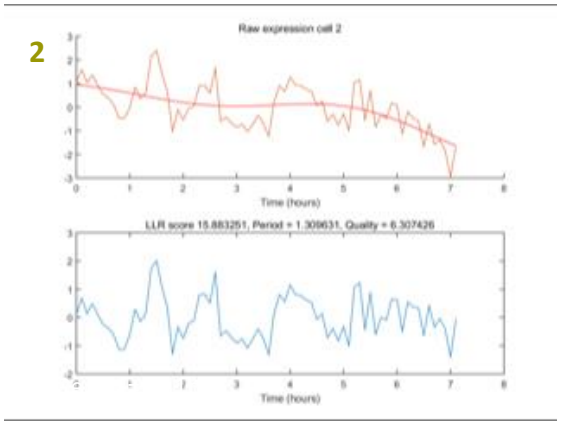
28°C

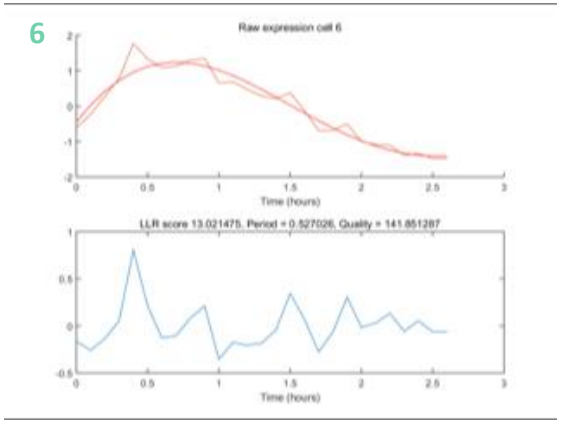


Lateral view



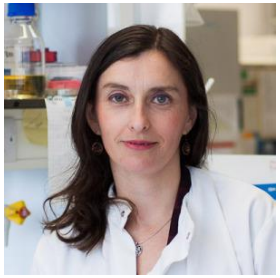




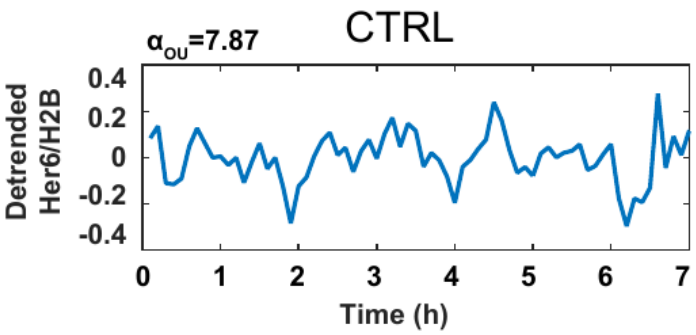


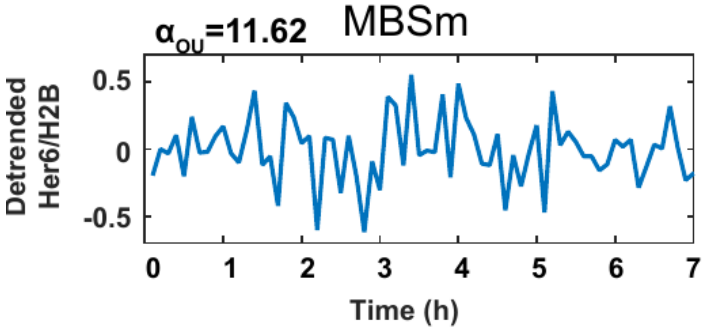
Analysed by Veronica Biga with method in Phillips et al., PLOS Comput Biol. 2017

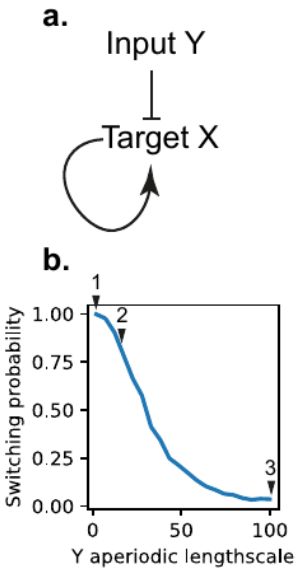
How are changes in gene expression dynamics interpreted downstream?

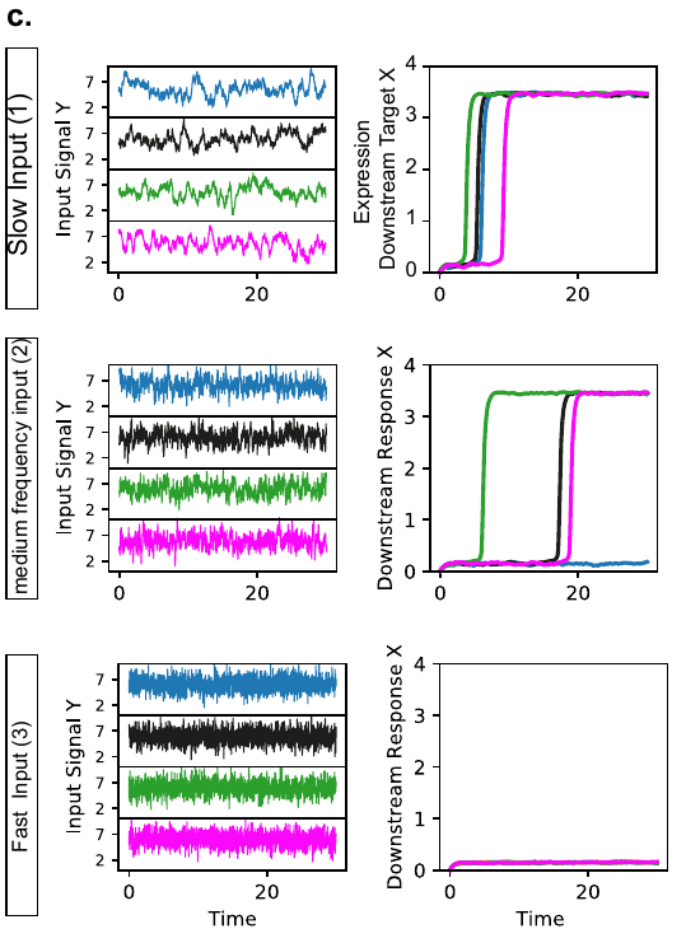


Ximena Soto









New biorxiv preprint!

Soto et al., **miR-9 mediated noise optimization of the her6 oscillator is needed for cell state progression in the Zebrafish hindbrain**

https://www.biorxiv.org/content/10.1101/608604v1

Next step: inference on dynamic data

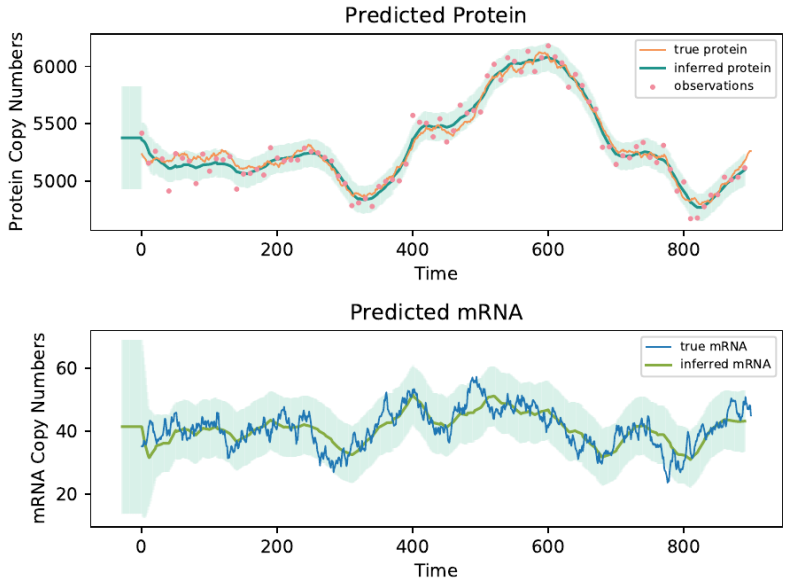
- Kalman filters can be used to infer parameters from *single traces* rather than summary statistics

Systems biology

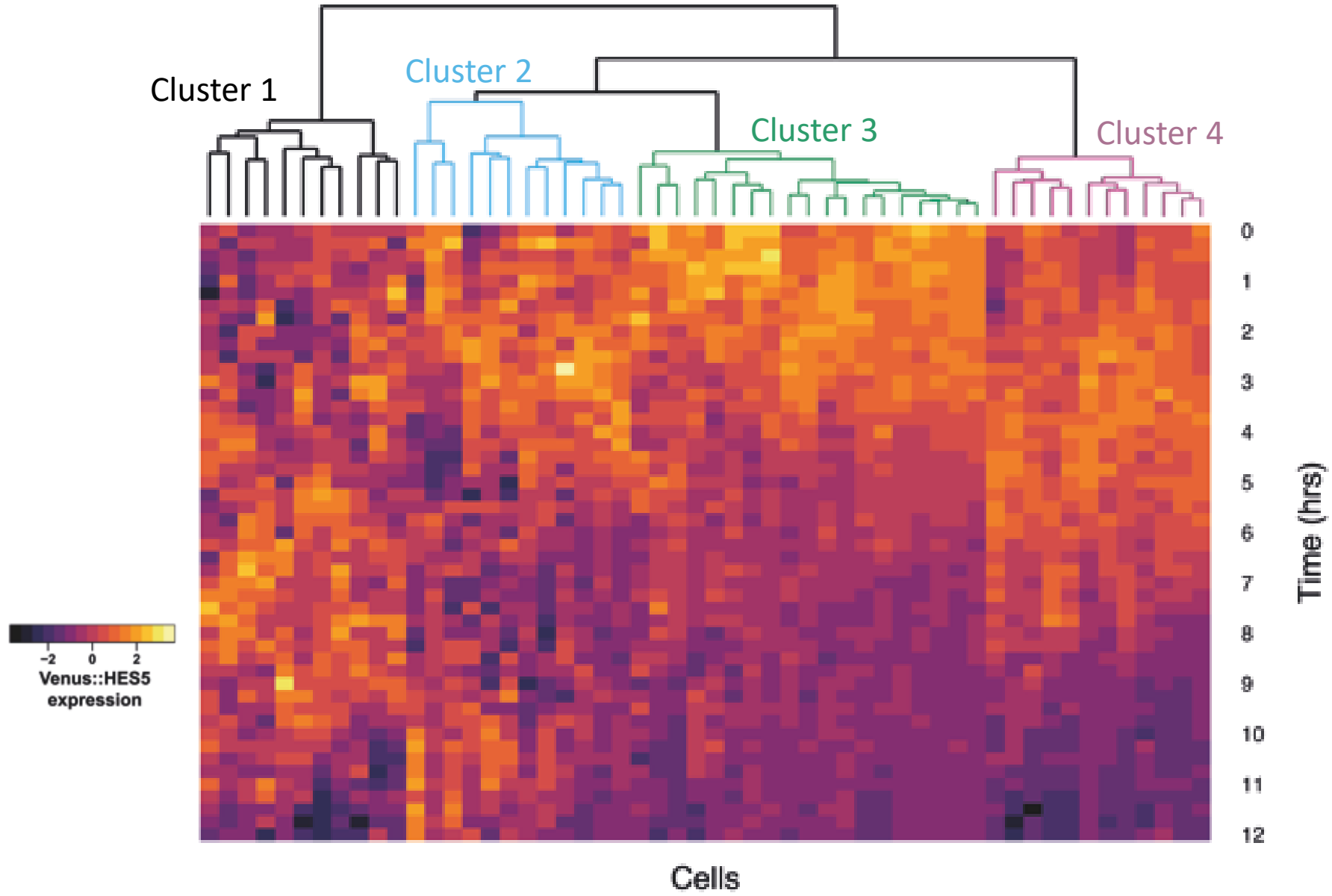
Filtering and Inference for stochastic oscillators with distributed delays

Silvia Calderazzo [1,2]*, Marco Brancaccio[3], and Bärbel Finkenstädt [1]*

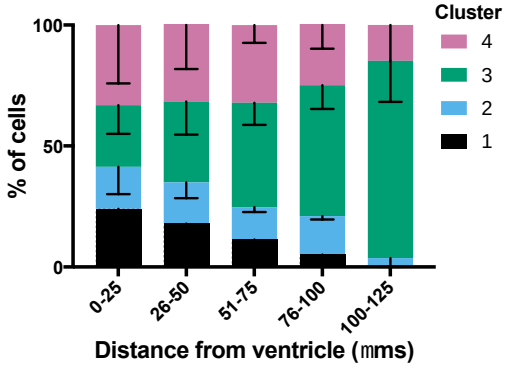
Joshua Burton

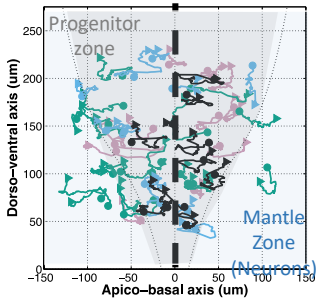


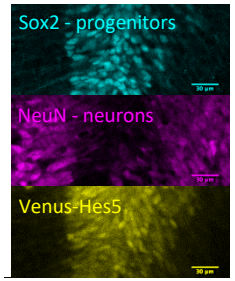
Distinct patterns of Venus-Hes5 dynamics can be identified using hierarchical clustering



Integrative analysis of live imaging data correlates cell position with cell state







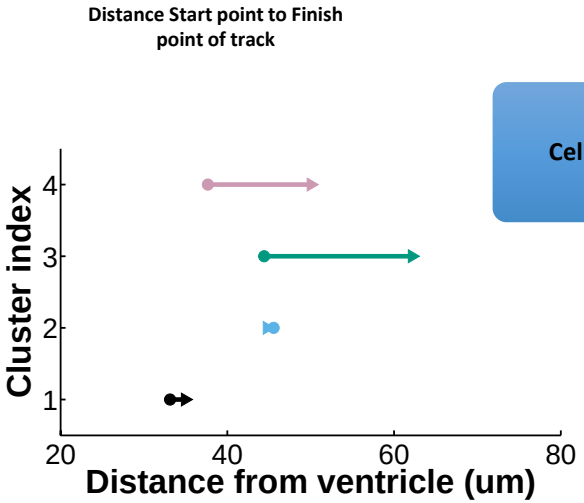
Molecular Markers

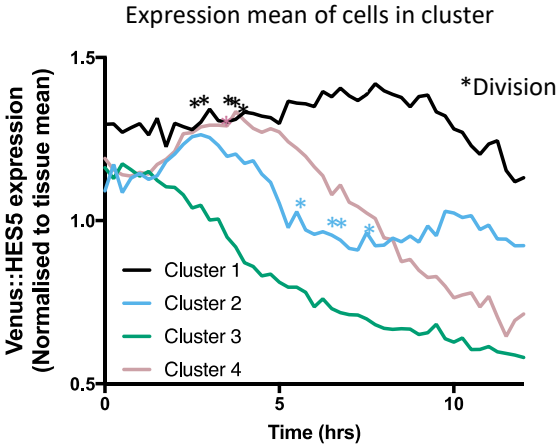
Cell position

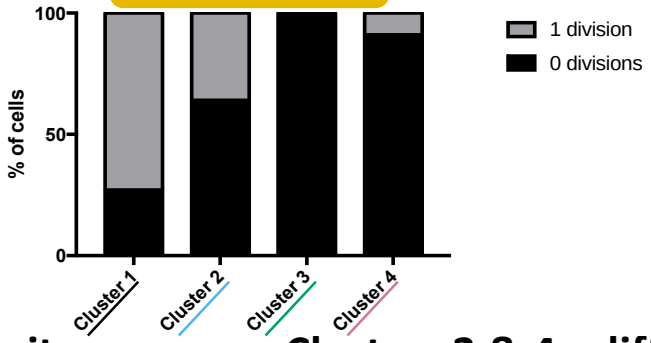
Cell movement

Dynamic gene expression

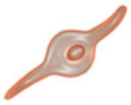
Cell Divisions

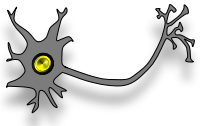






HES5 high



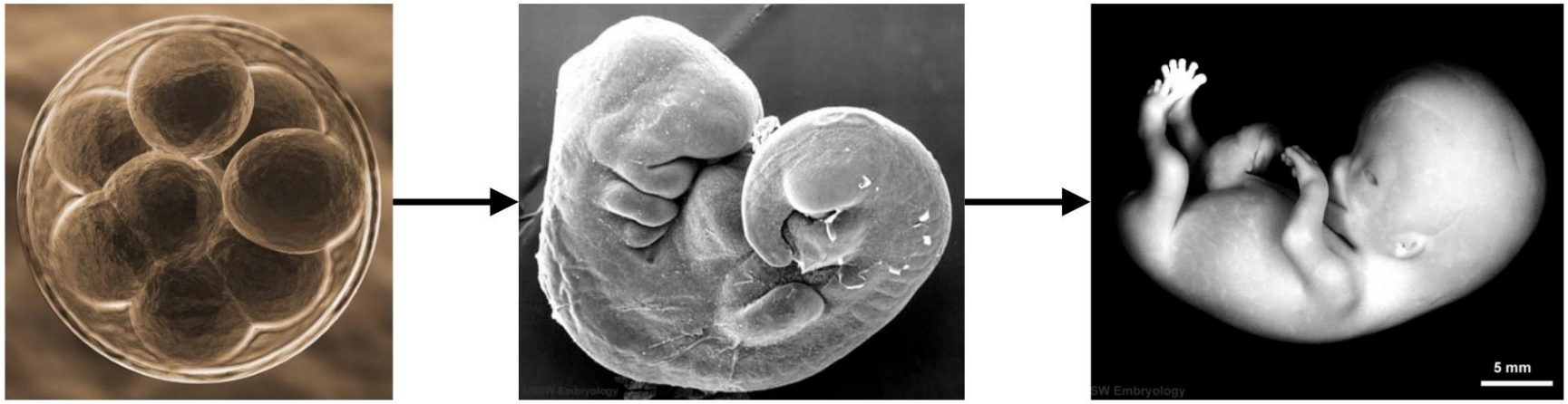


Declining HES5

Clusters 1 & 2 - dividing progenitors

Clusters 3 & 4 - differentiating into neurons

Developmental biology can be described and understood with the help of mathematics



- To elucidate the rules governing embryonic development
  - Need to understand the interplay of many processes: biophysical constraints, molecular signalling, gene expression dynamics etc.
- Aim: closely integrate theoretical tools with experimental data to unravel key phenomena that underly morphogenesis