Decoding Underlying Behaviour from Destructive Time Series Experiments through Gaussian Process Models

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Molecular biology time series

- Biological systems are dynamic, observing their time evolution very helpful
- Time series measurements of gene expression, protein activity, protein binding, ...
- Problem: most of these assays are highly disruptive to the sample
- Therefore: time series = series of independent experiments run for different lengths of time
- This has implications for modelling...

Outline

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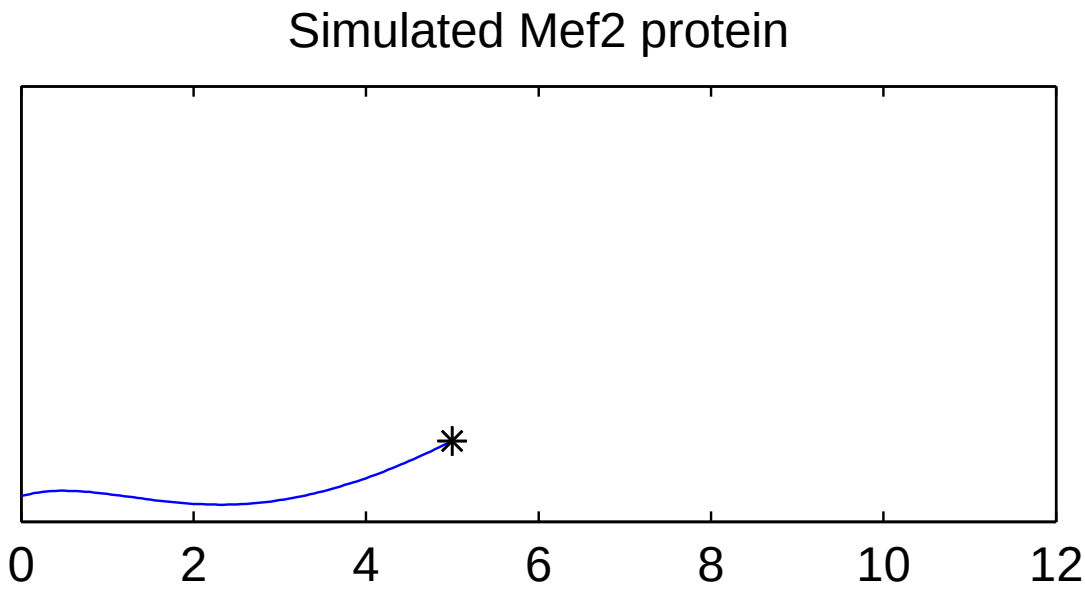
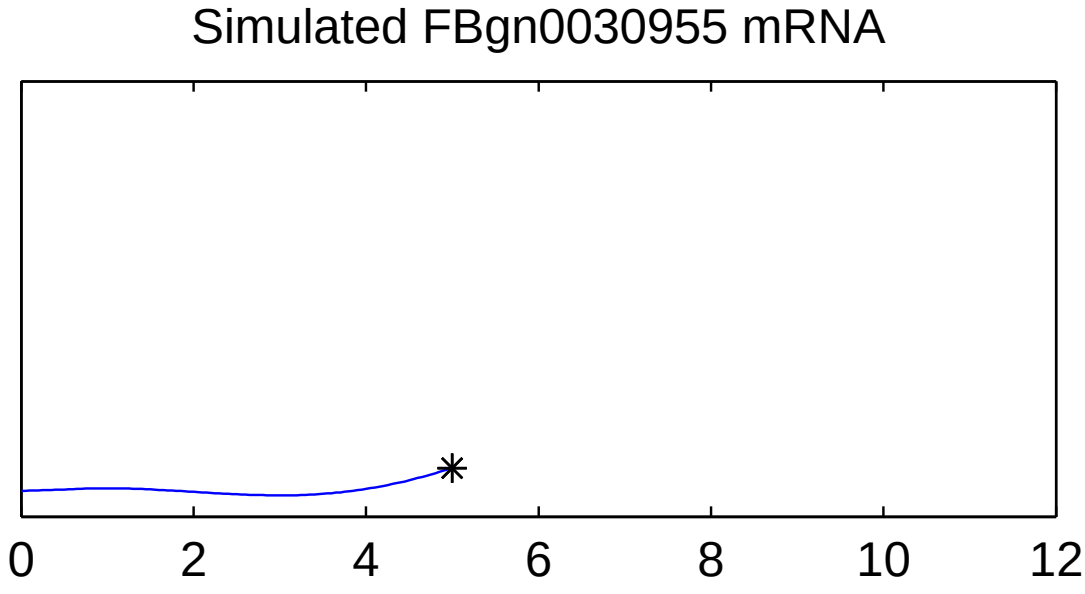
Simulated molecular biology time series





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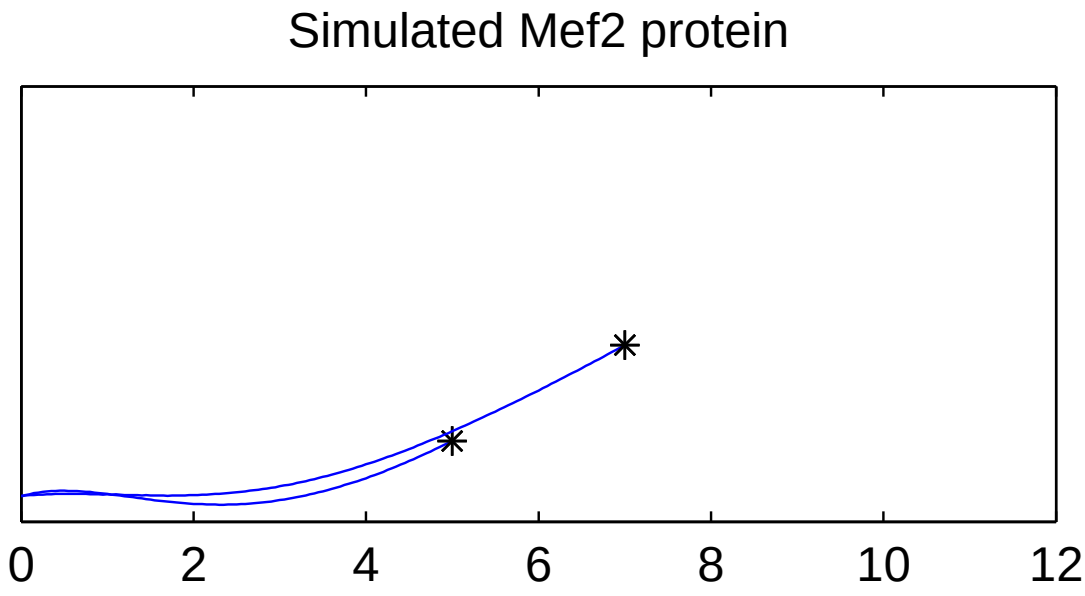

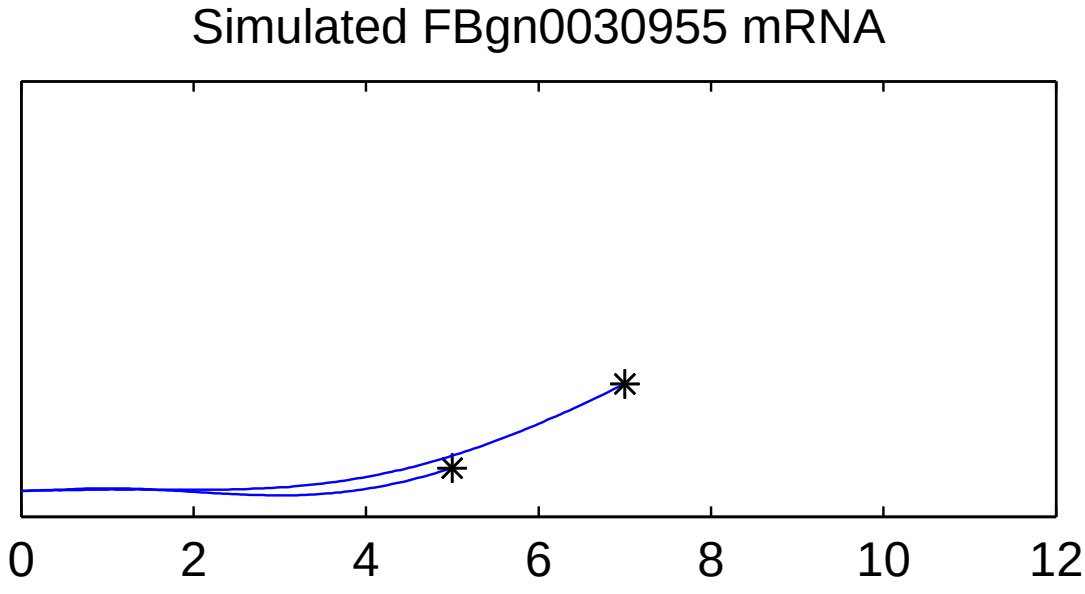

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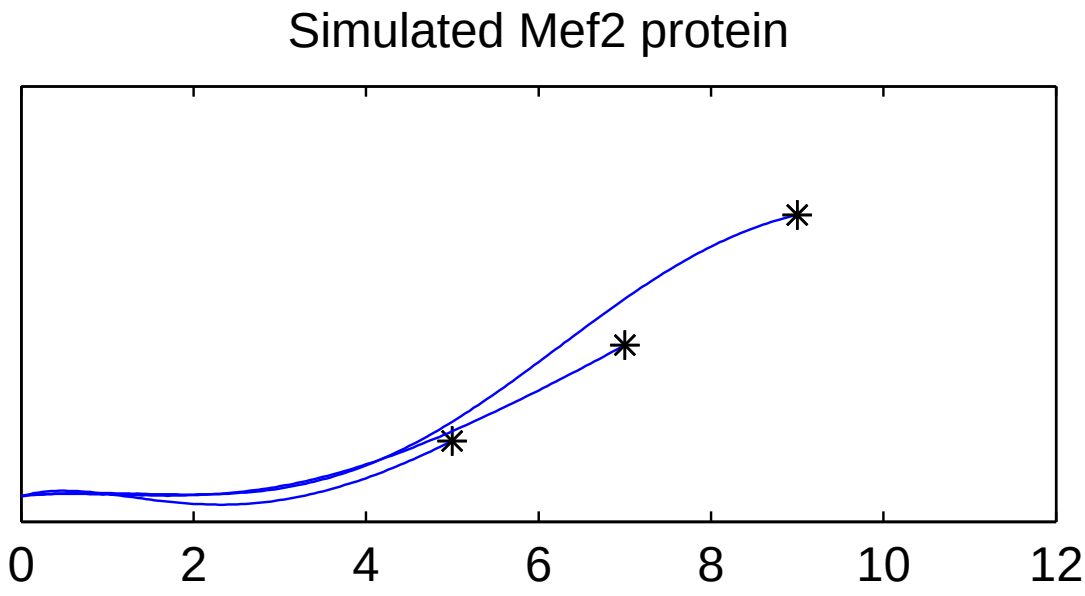

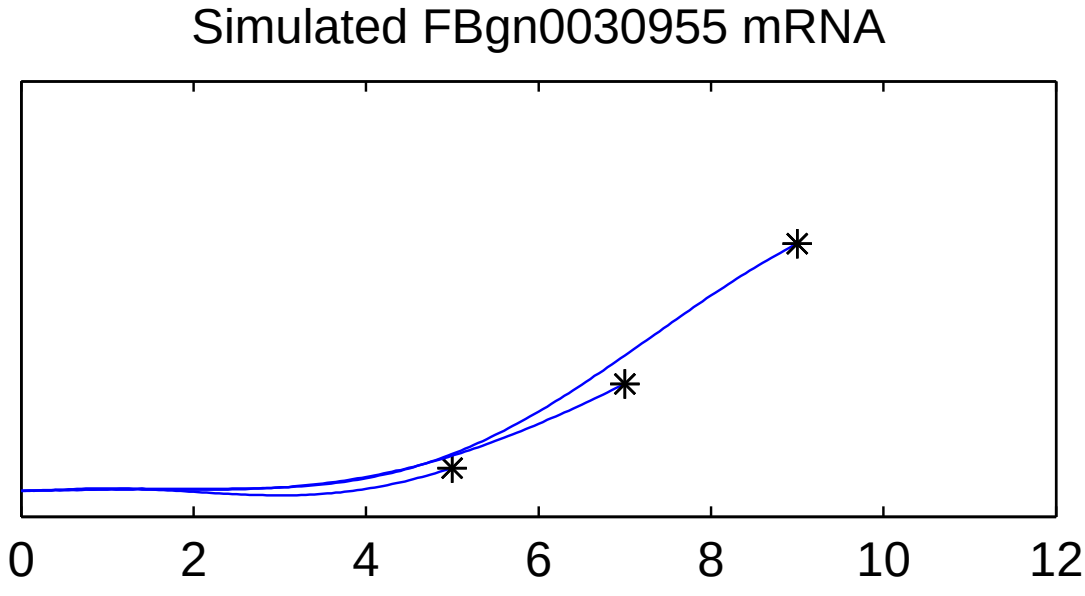

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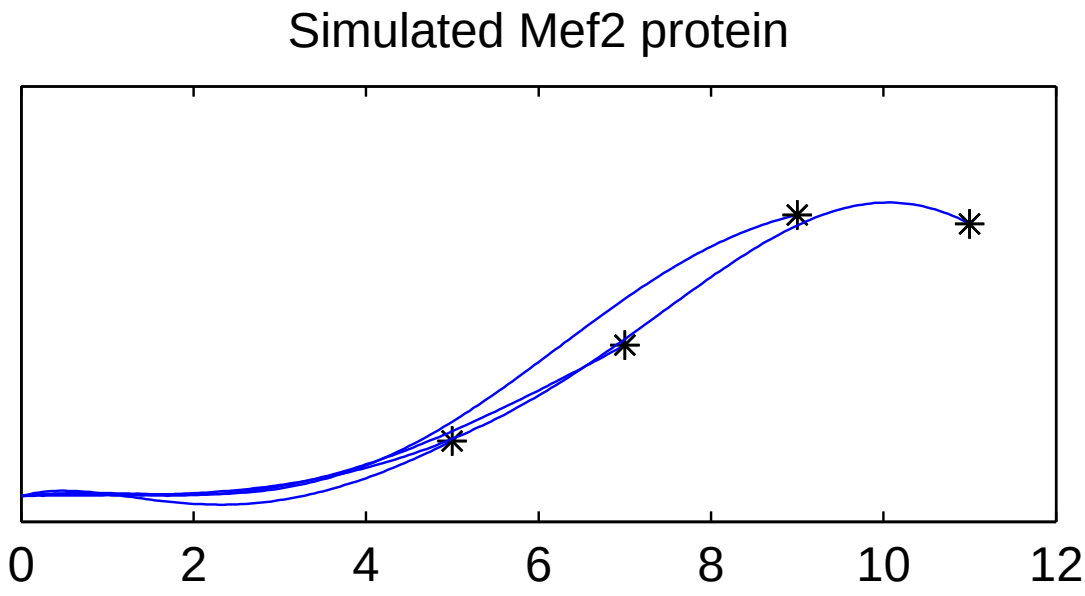

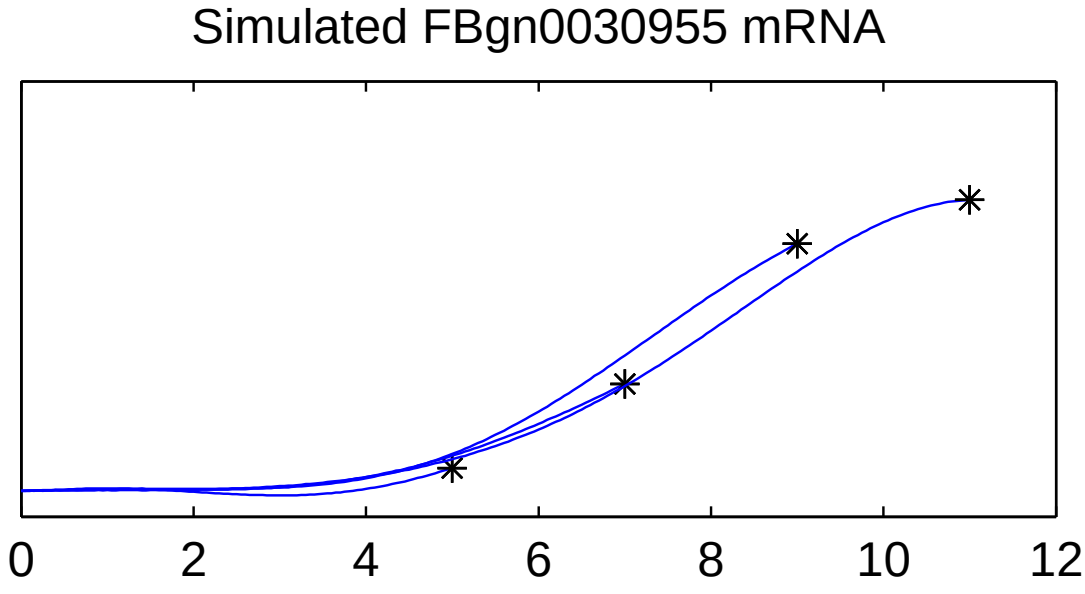

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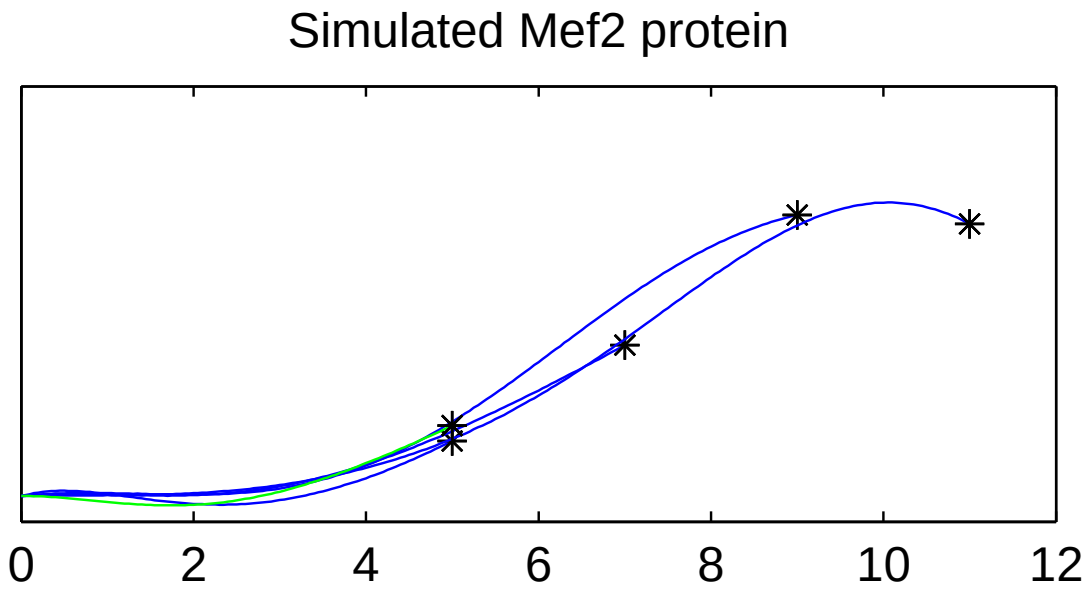

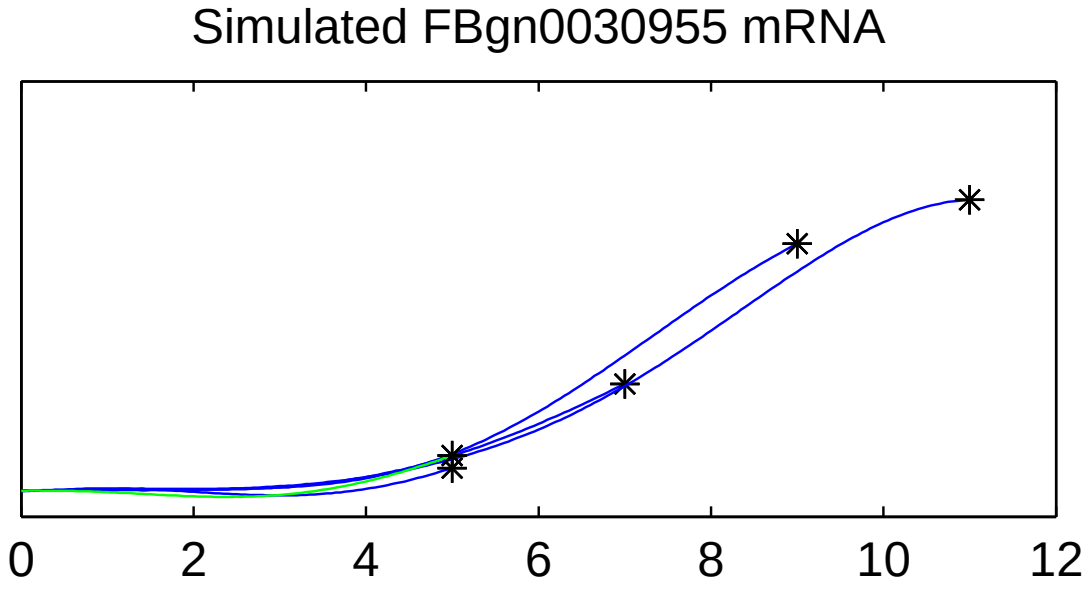

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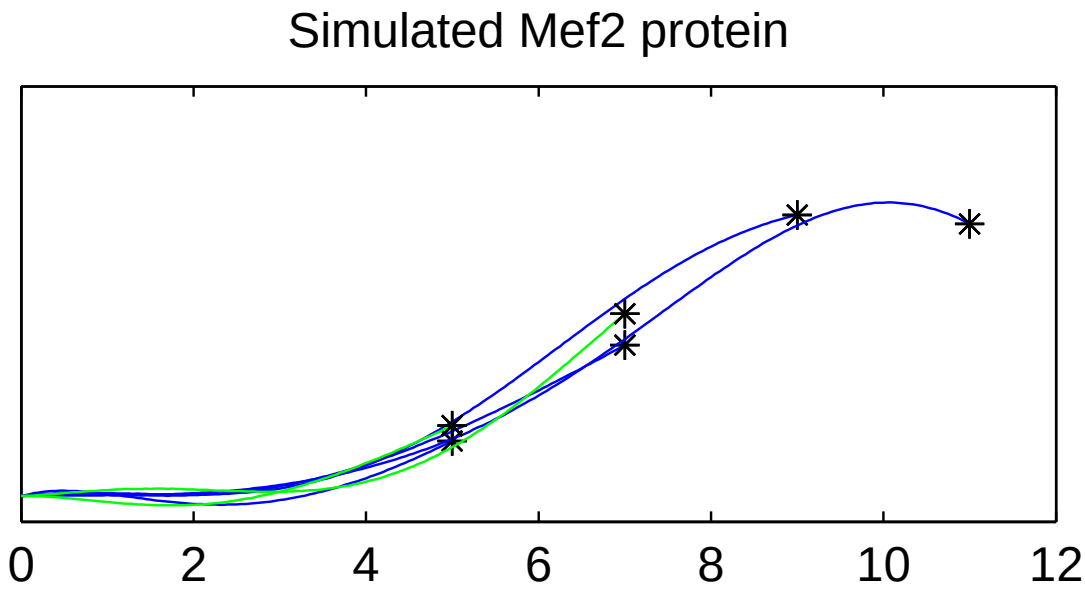

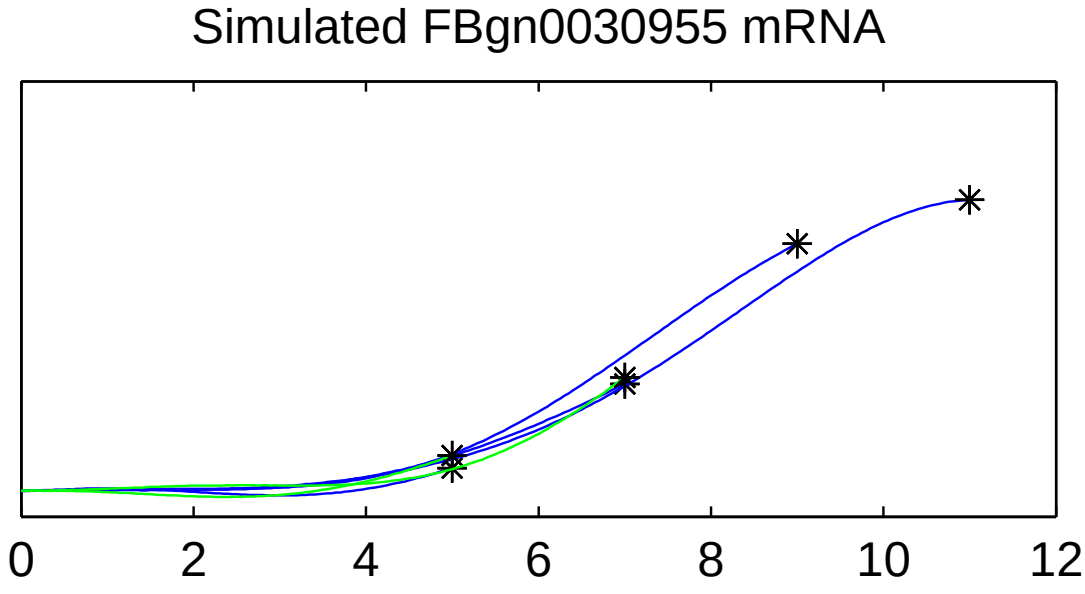

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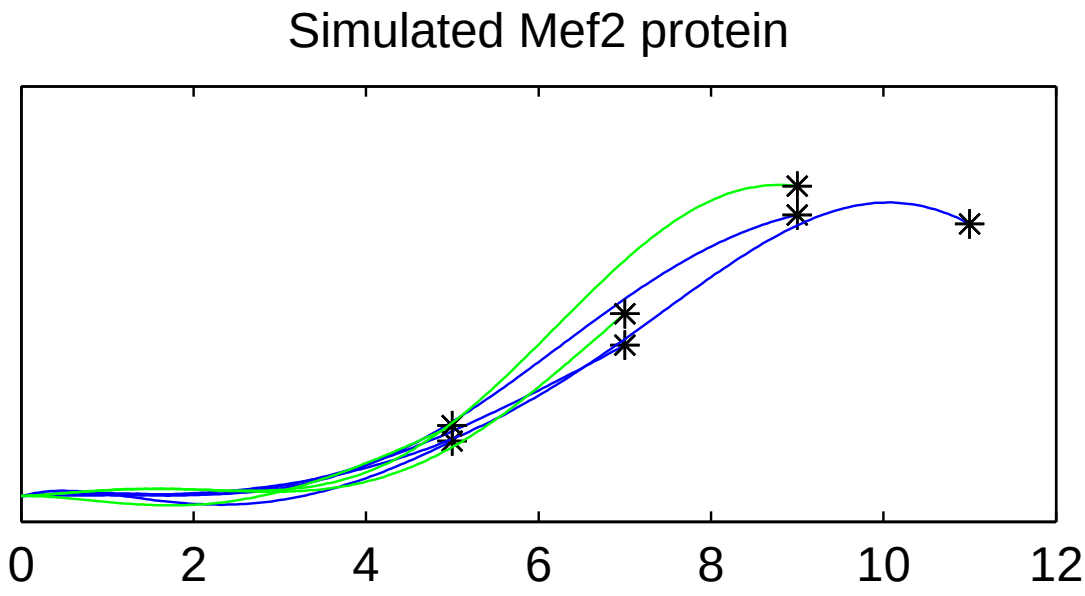

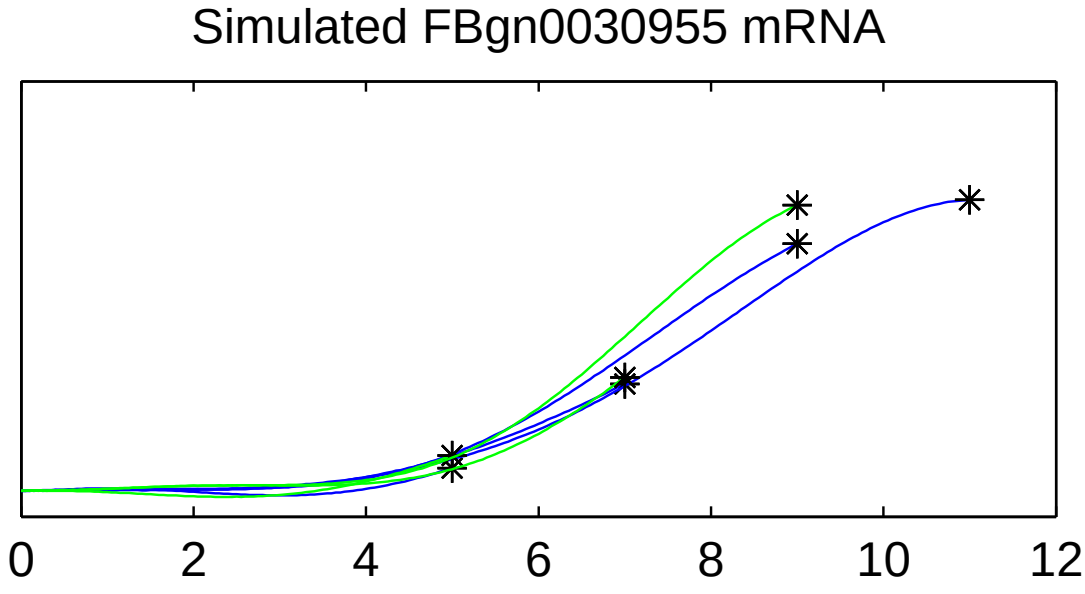

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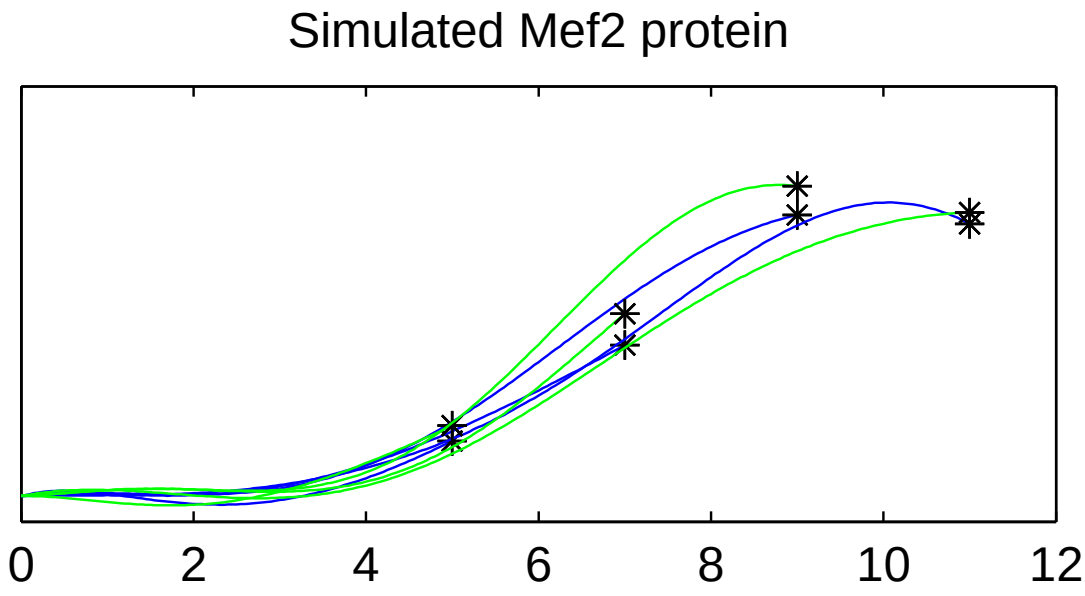

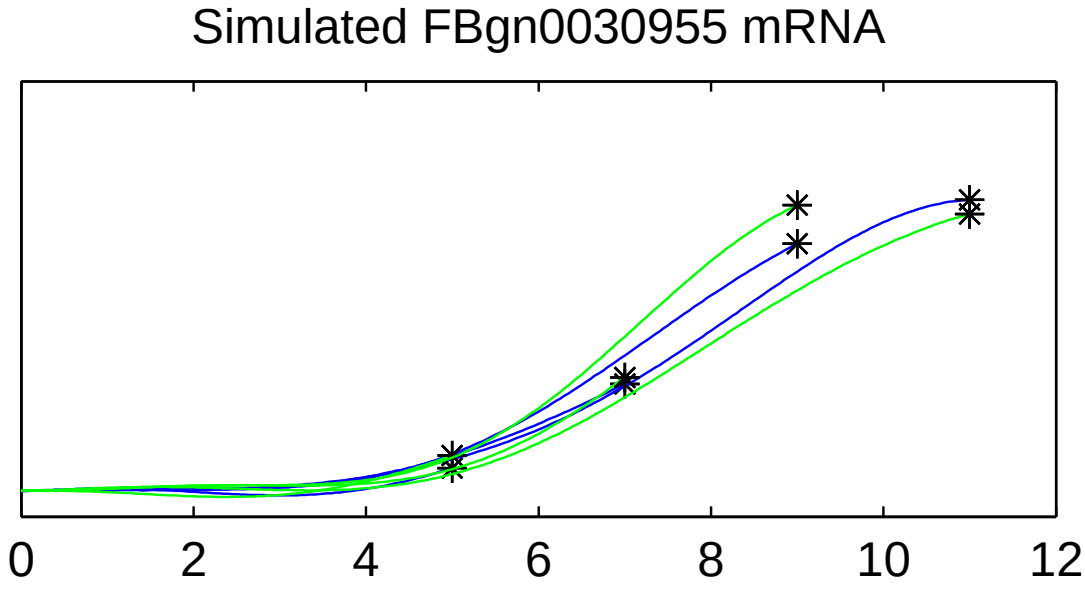

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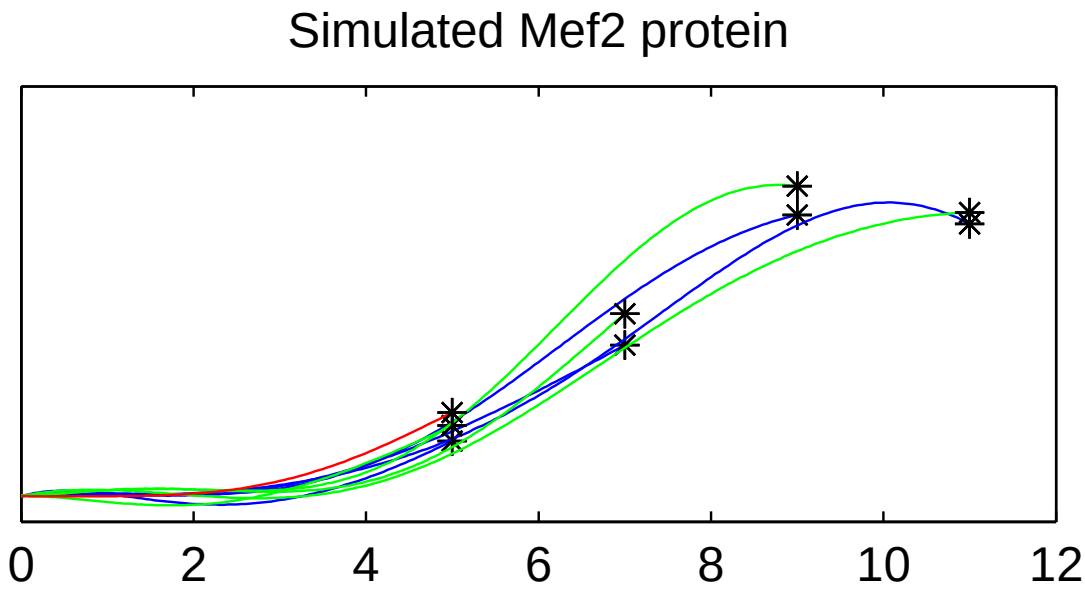

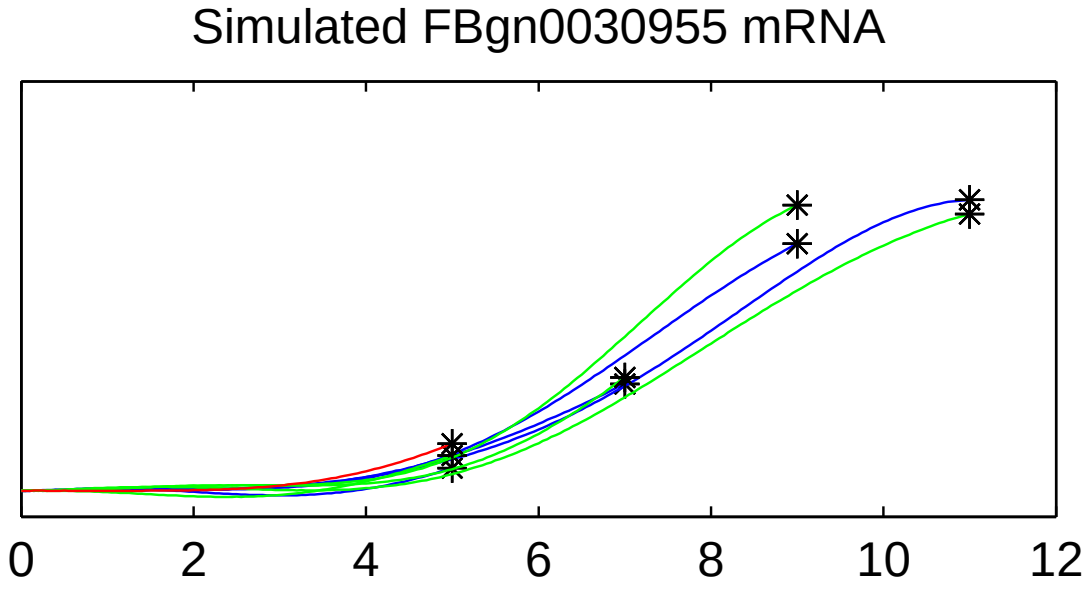

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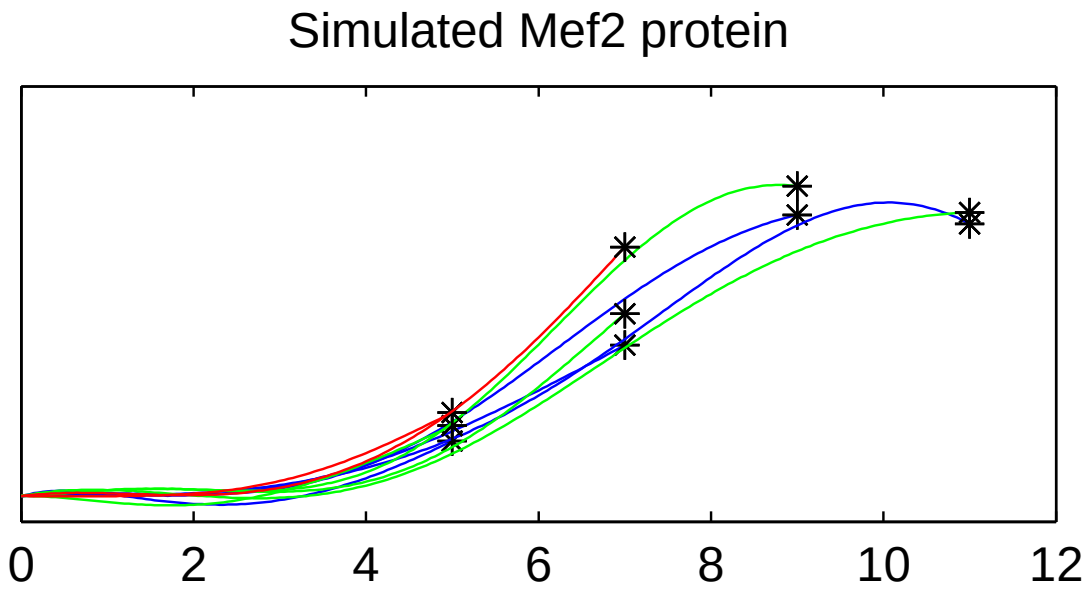

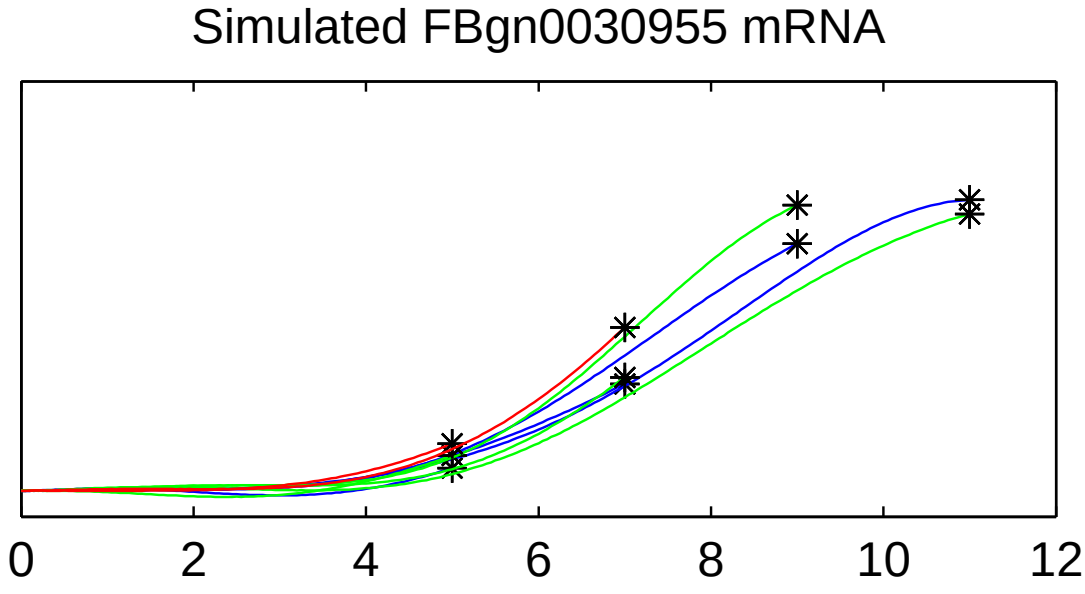

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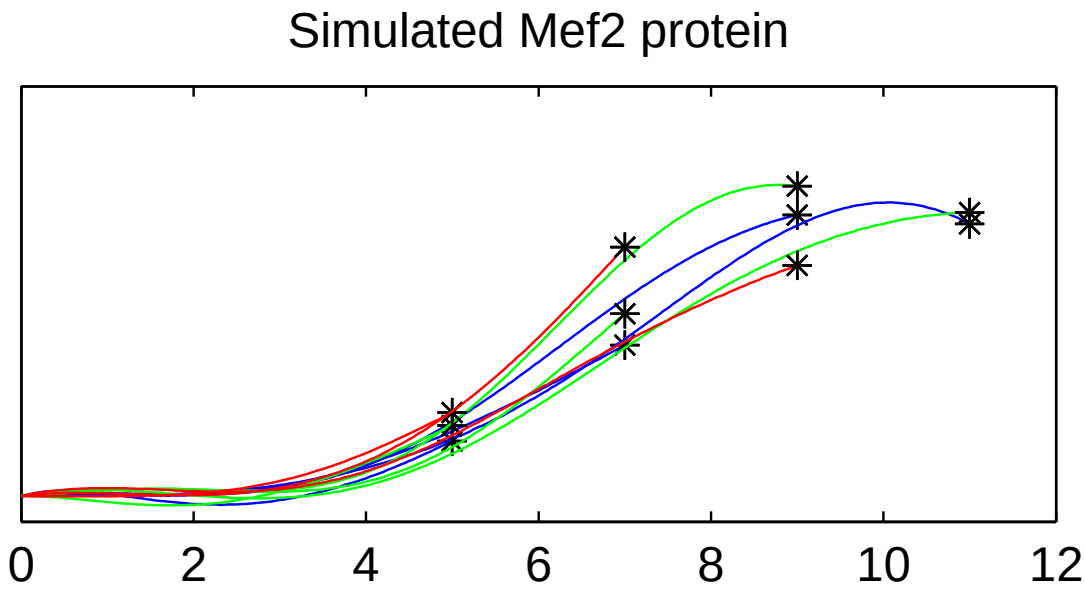

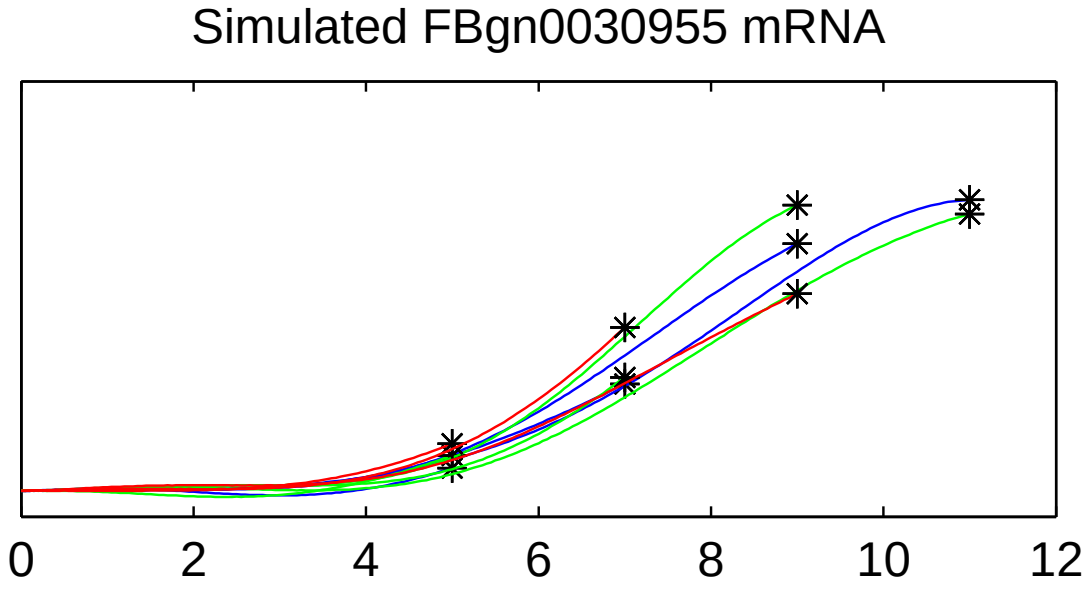

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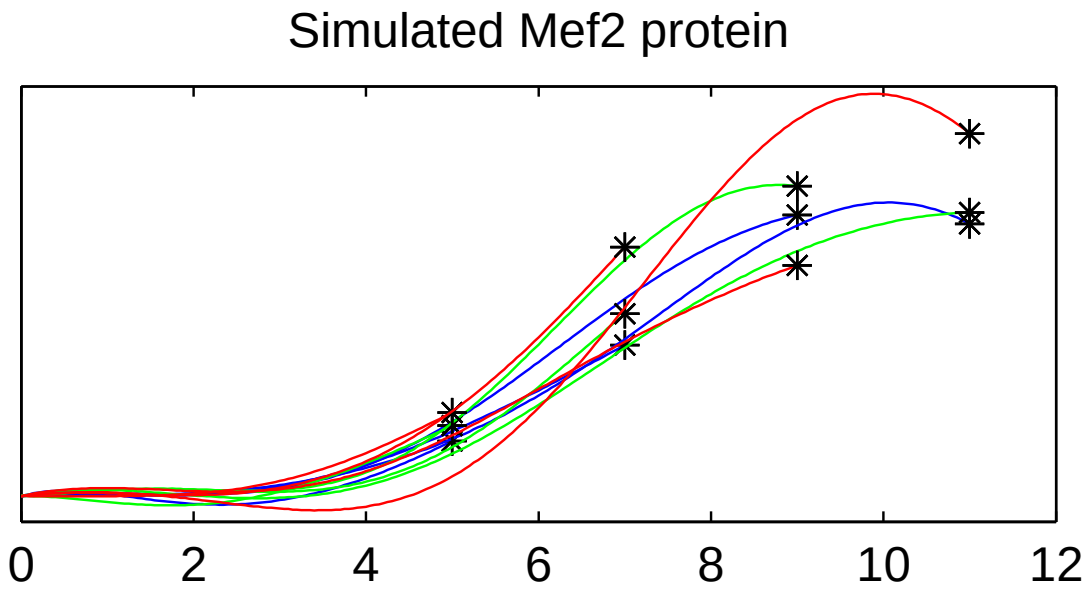
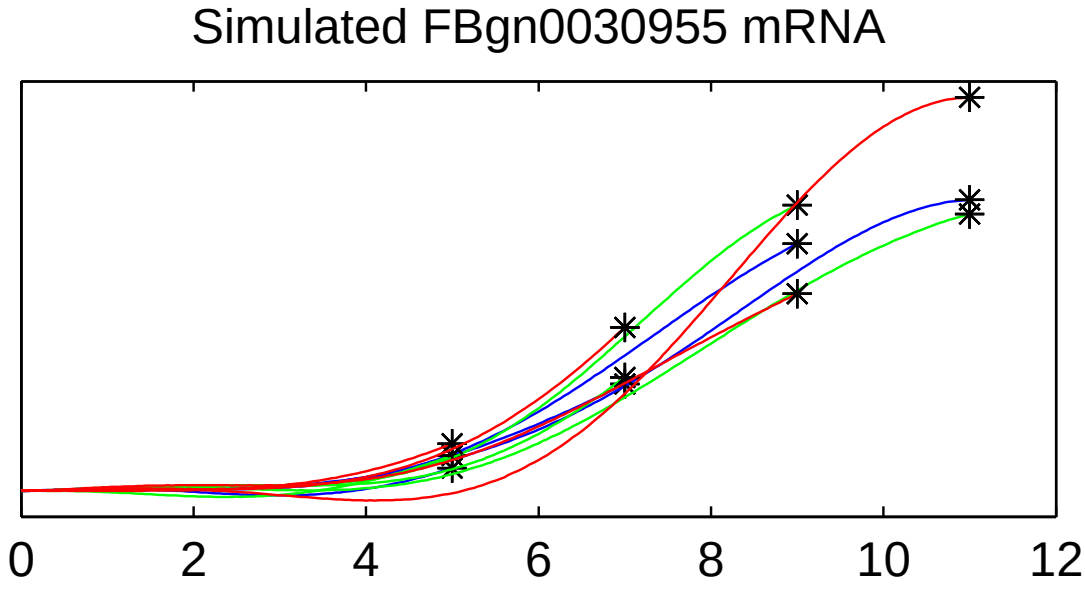
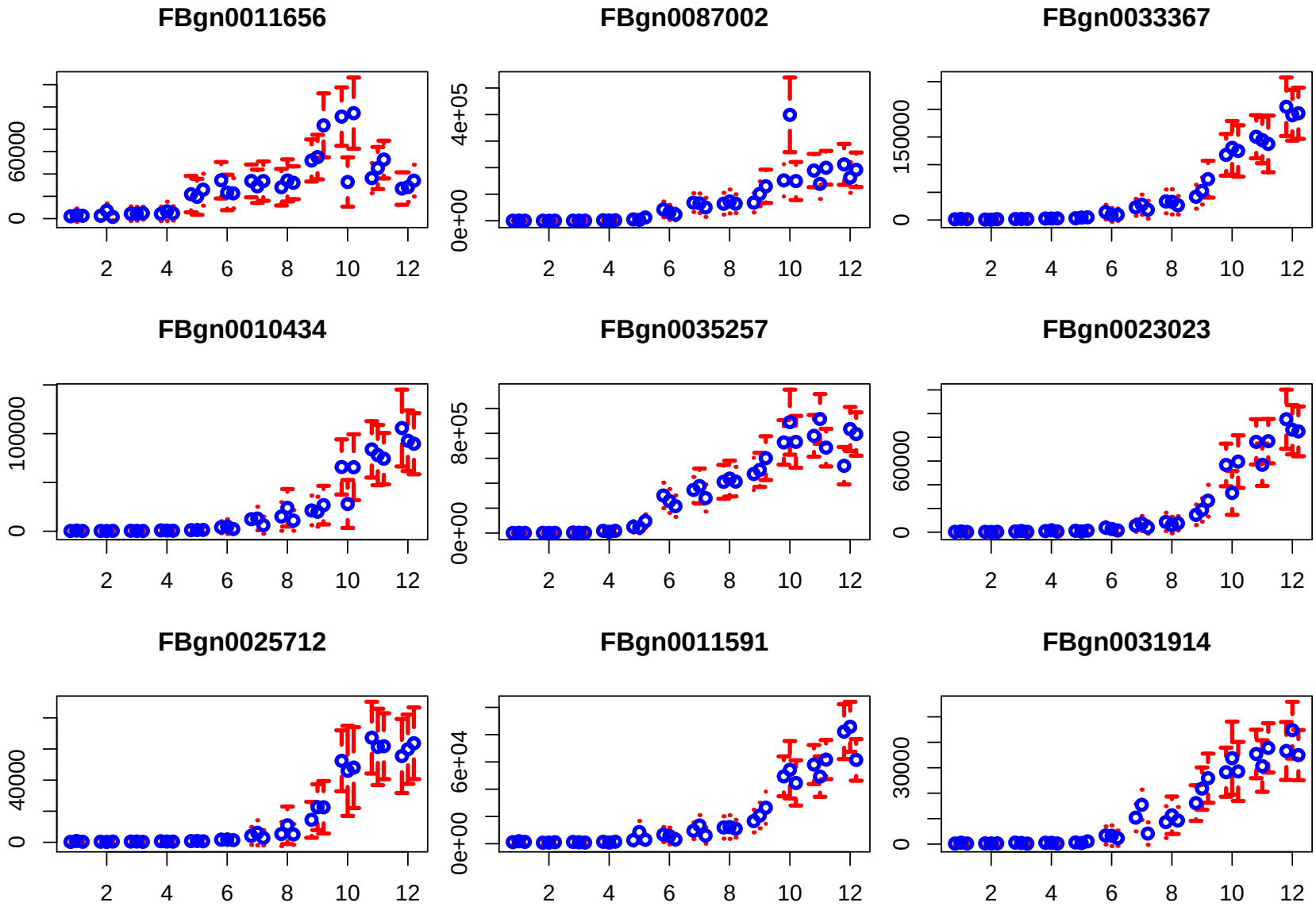




Real gene expression time series



Outline

Example model: Linear ODE model of transcription

- Linear Activation Model (Barenco et al., 2006, Genome Biology)

$$\frac{\mathrm{d}x_j(t)}{\mathrm{d}t} = B_j + S_j f(t) - D_j x_j(t)$$

- $x_j(t)$ – concentration of gene j's mRNA
- $f(t)$ – concentration of active transcription factor
- Model parameters: baseline B_j, sensitivity S_j and decay D_j
- Placing a Gaussian process (GP) prior on $f(t)$ leads to a joint GP over all concentration profiles (Gao et al., 2008, Bioinformatics)

How to connect the model to data?

1. Assume independent profiles for each complete (biological) repeat
   - Loses statistical power for extra independence assumptions
   - Is it meaningful to order the repeats?
2. Assume one shared underlying profile with independent observations
   - Potentially sensitive to outliers

Exchangeability analysis

Assume $x_j^k(t_i)$ observation of kth repeat of jth gene at ith time

	$x_\cdot^k(t_i) \leftrightarrow x_\cdot^{k'}(t_i)$ "swap arrays"	$x_j^k(t_i) \leftrightarrow x_j^{k'}(t_i)$ "swap single gene"
"Reality"	Yes	No
1. Independent profiles	No	No
2. Shared profile	Yes	Yes

Solution: hierarchical GP model

- Assume the underlying $f(t)$ is composed of a shared and an experiment-specific part $f_{ik}(t)$

$$\frac{\mathrm{d}x_j(t)}{\mathrm{d}t} = B_j + S_j[f_{\text{shared}}(t) + f_{ik}(t)] - D_j x_j(t)$$

- Covariance is of the same form as usual
- Introduces additional covariance terms for measurements from the same experiment
- Alternative parametrisations of variance of $f_{ik}(t)$
  - Shared across all experiments
  - Sampled independently for each experiment

Exchangeability analysis revisited

Assume $x_j^k(t_i)$ observation of kth repeat of jth gene at ith time

	$x_\cdot^k(t_i) \leftrightarrow x_\cdot^{k'}(t_i)$ "swap arrays"	$x_j^k(t_i) \leftrightarrow x_j^{k'}(t_i)$ "swap single gene"
"Reality"	Yes	No
1. Independent profiles	No	No
2. Shared profile	Yes	Yes
3. Hierarchical model	Yes	No

Outline

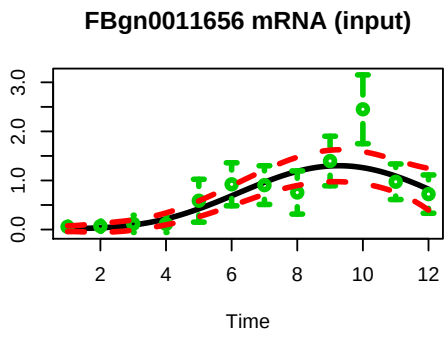
ODE model of translation and transcription

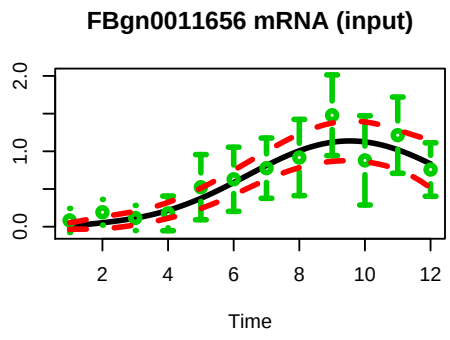
- Assume TF is transcriptionally regulated with related mRNA $y(t)$
- This yields a system of ODEs (Gao et al., 2008)

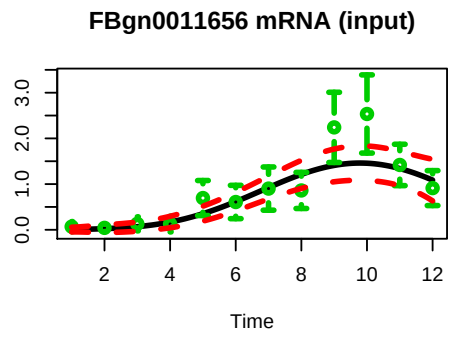
$$\frac{\mathrm{d}f(t)}{\mathrm{d}t} = \sigma y(t) - \delta f(t)$$
$$\frac{\mathrm{d}x_j(t)}{\mathrm{d}t} = B_j + S_j f(t) - D_j x_j(t)$$

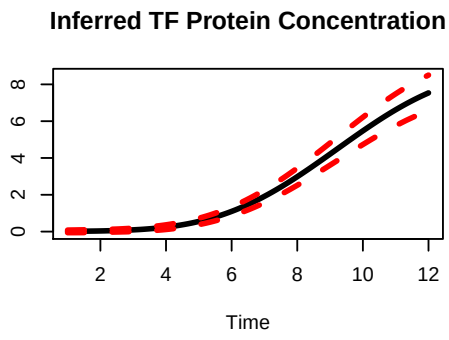
- The corresponding GP model can be derived analogously to the previous case

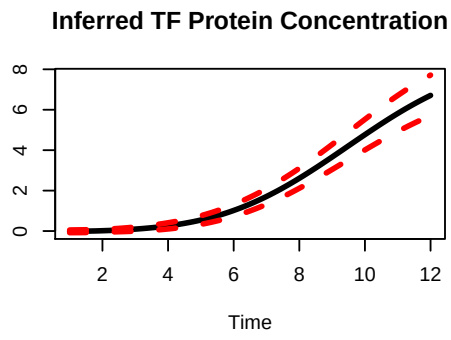
Independent profiles

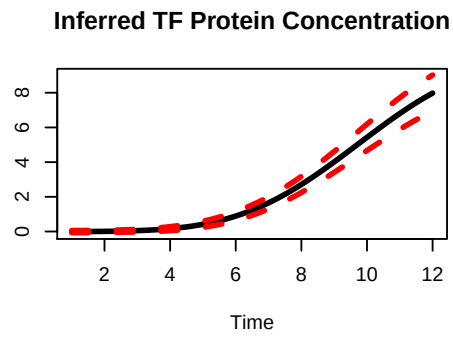


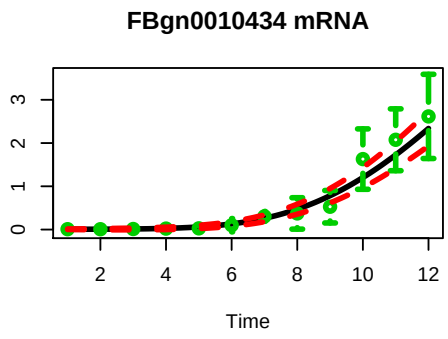


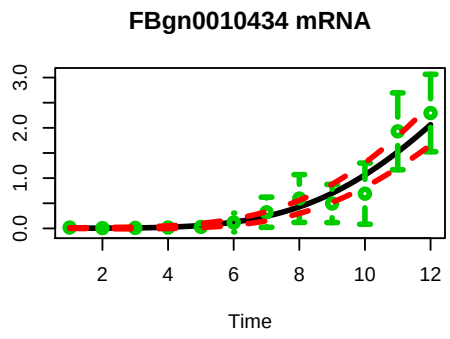


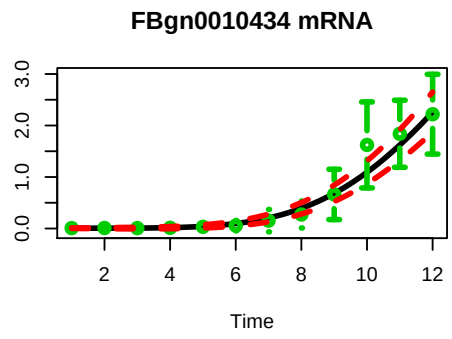




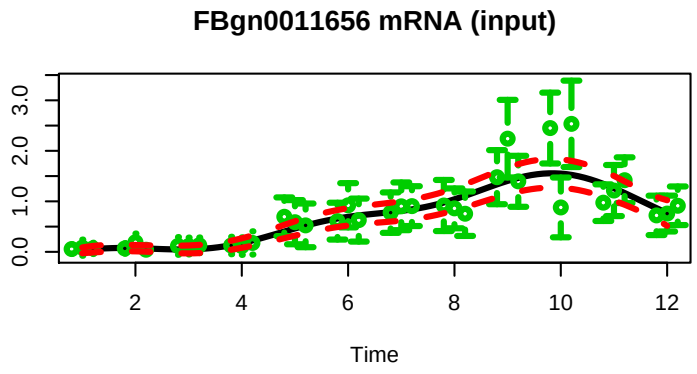


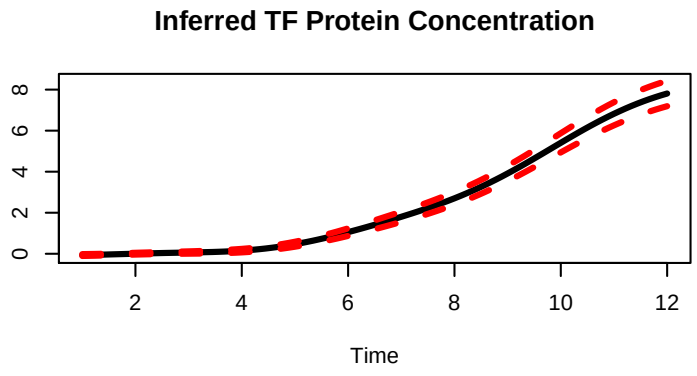


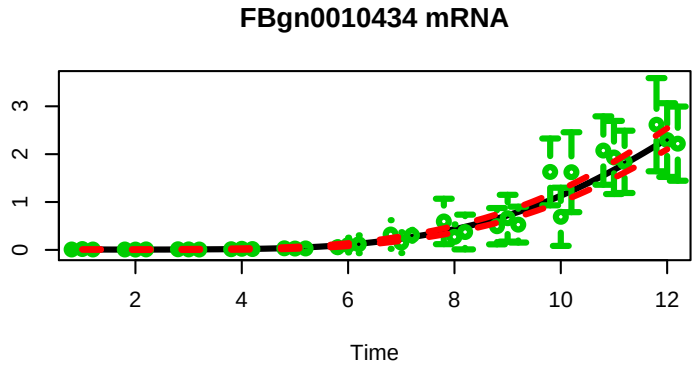




Hierarchical model







Conclusion

- Previous models of time series expression data are wrong
  - Invalid exchangeability assumptions
- Proposed hierarchical model rectifies this
- Open problems / work in progress
  - Need to move beyond Gaussian likelihoods?
  - How to do MCMC in these models?

Acknowledgements

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Coming soon to Bioconductor:

tiger — Transcription factor Inference through Gaussian process Expression Reconstruction

References

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