

Modelling of X-Chromosome reactivation by Toggle switch

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Introduction

Origin of X-Chromosome inactivation & upregulation

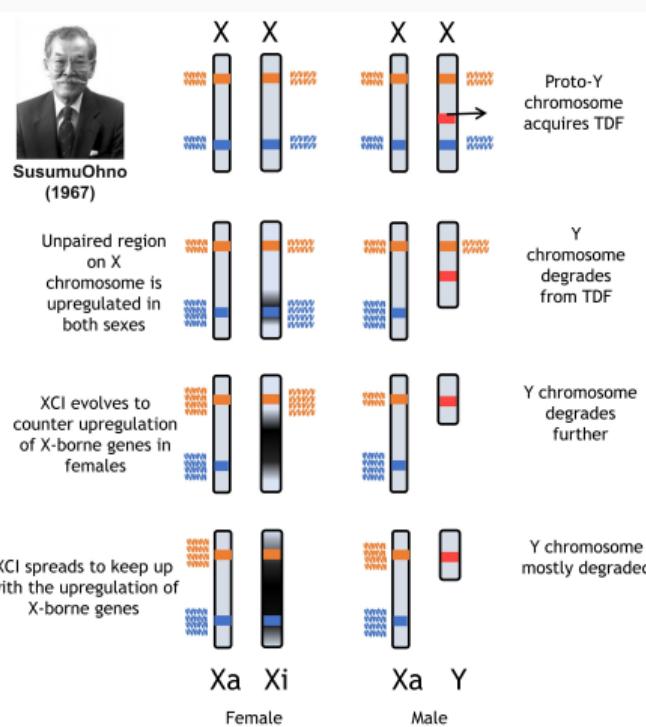


Figure 1: Ohno's hypothesis for X-Chromosome upregulation^{1 2}

¹ "Sex Chromosomes and Sex-linked Genes.", 1968.

²Credits: Srimonta Gayen

Mechanism of X-Chromosome upregulation

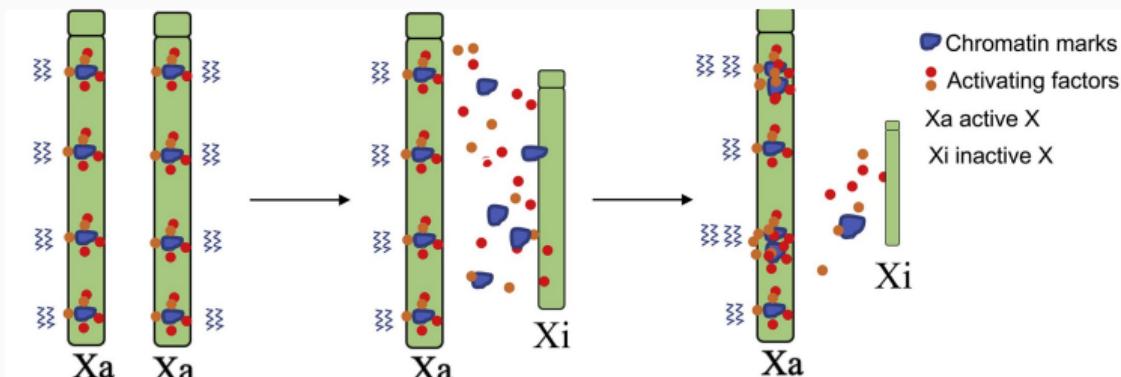


Figure 2: Model describing a mechanism of X-Chromosome upregulation^{3 4}

³Naik et al., 2022.

⁴Credits: Kishore Hari

Occurrence of X-chromosome reactivation

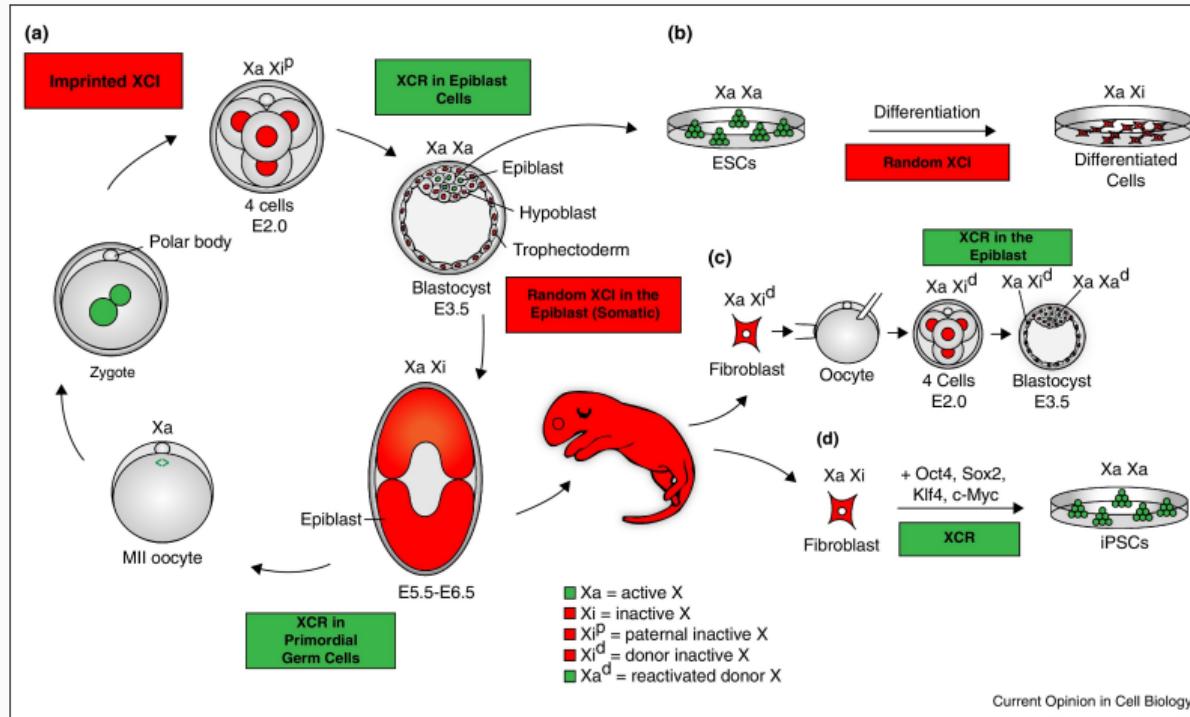


Figure 3: X-Chromosome reactivation in mouse embryo and iPSC cells^{5 6}

⁵ Pasque and Plath, 2015.

⁶ Image used from article

Complete reactivation of X-Chromosome

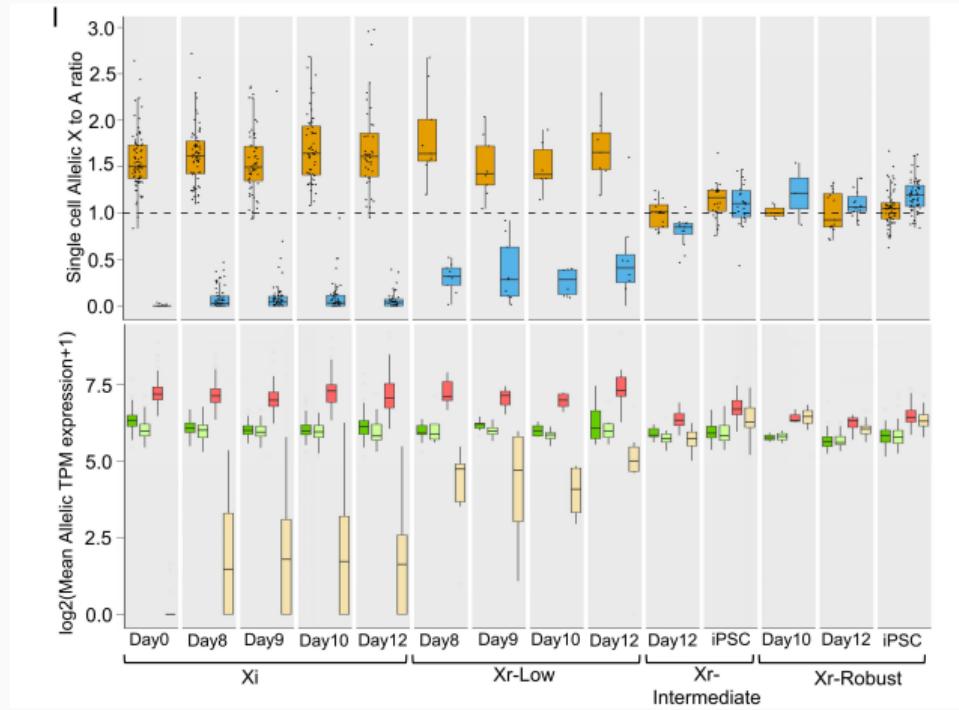


Figure 4: Erasure of X-upregulation on complete reactivation ⁷

⁷Credits: Hemant C. Naik

Partial reactivation of X-Chromosome

F

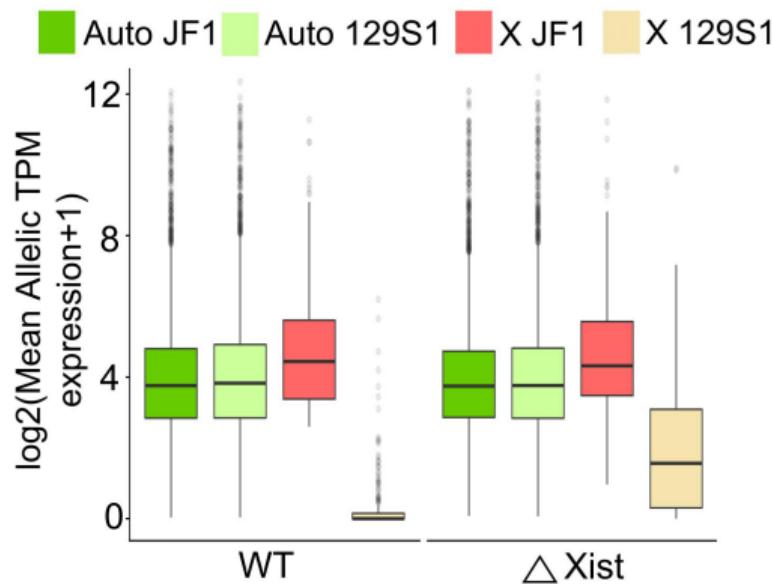
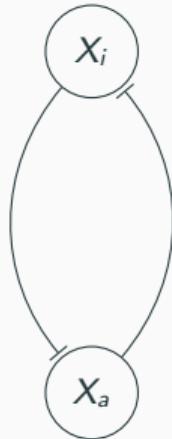


Figure 5: X-upregulation still present on partial reactivation ⁸

⁸Credits: Hemant C. Naik

Motivation



- Systems biology approach
- Toggle switch = Bistable
- Connections influence phenotypes^a
- Simple phenomenological model

^aChauhan et al., 2021.

Figure 6: Mutual inhibition?

Methods

Modelling Topologies

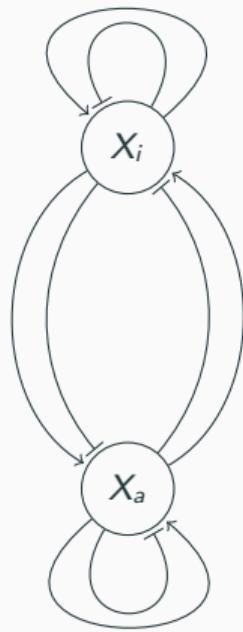
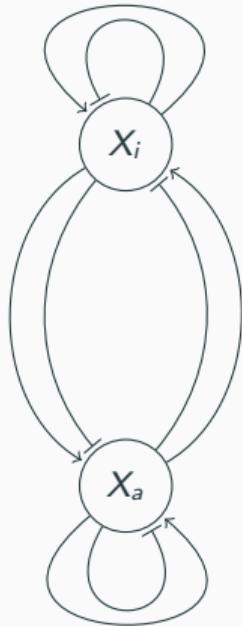


Figure 7: Possible topologies

Modelling Topologies

Differential equations



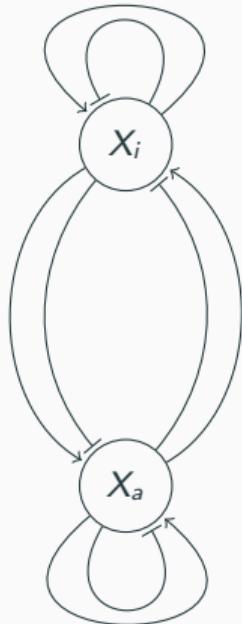
$$\frac{dX_i}{dt} = \underbrace{a_1 f(K_1, X_a, n)}_{\text{cross}} + \underbrace{b_1 f(K_3, X_i, n)}_{\text{self}} - \underbrace{c_1 X_i}_{\text{decay}} \quad (1)$$

$$\frac{dX_a}{dt} = \underbrace{a_2 f(K_2, X_i, n)}_{\text{cross}} + \underbrace{b_2 f(K_4, X_a, n)}_{\text{self}} - \underbrace{c_2 X_a}_{\text{decay}} \quad (2)$$

$$f \in \{f_a, f_i, f_n\}$$

Figure 7: Possible topologies

Modelling Topologies



Differential equations

$$\frac{dX_i}{dt} = \underbrace{a_1 f(K_1, X_a, n)}_{\text{cross}} + \underbrace{b_1 f(K_3, X_i, n)}_{\text{self}} - \underbrace{c_1 X_i}_{\text{decay}} \quad (1)$$

$$\frac{dX_a}{dt} = \underbrace{a_2 f(K_2, X_i, n)}_{\text{cross}} + \underbrace{b_2 f(K_4, X_a, n)}_{\text{self}} - \underbrace{c_2 X_a}_{\text{decay}} \quad (2)$$

$$f \in \{f_a, f_i, f_n\}$$

Activation:

$$f_a(X, K, n) = \frac{X^n}{K^n + X^n} \quad (3)$$

Inhibition:

$$f_i(X, K, n) = \frac{K^n}{K^n + X^n} \quad (4)$$

No effect

$$f_n(X, K, n) = 0 \quad (5)$$

Figure 7: Possible topologies

Fitting technique

- Take random values for parameters
- Solve differential equations
- Calculate sum of square error (residuals)
- Run differential evolution algorithm to minimize this value

Results

Testing cross connections w/ fixed self-activation

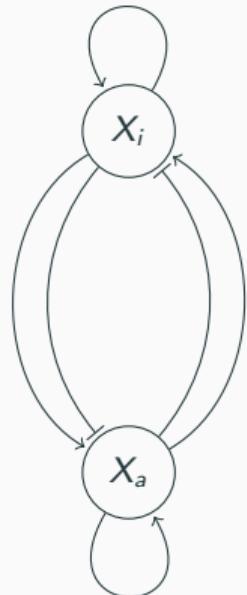


Figure 8: Cross connections

Testing cross connections w/ fixed self-activation

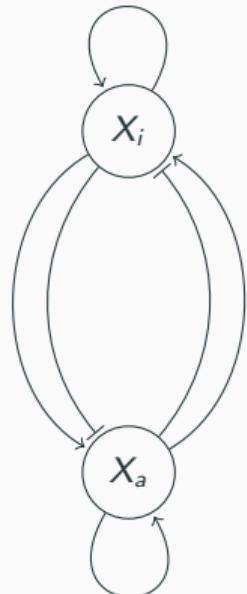
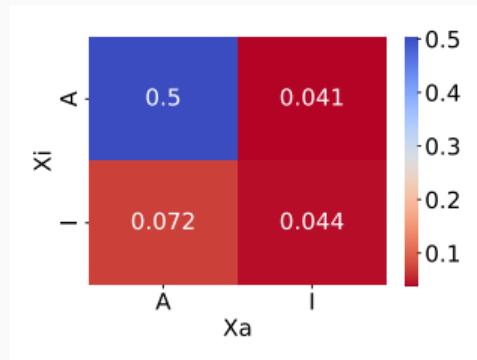
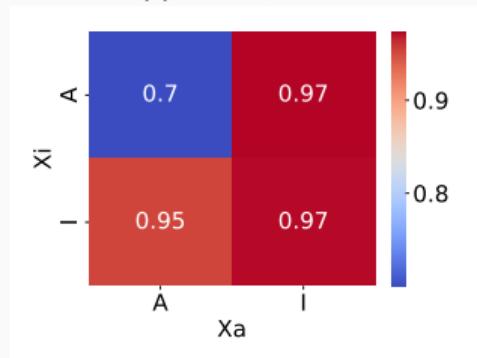


Figure 8: Cross connections



(a) Sum of square error



(b) R^2 values

Figure 9: Full reactivation

Testing cross connections w/ fixed self-activation

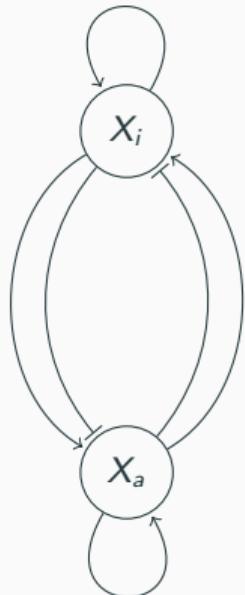


Figure 8: Cross connections

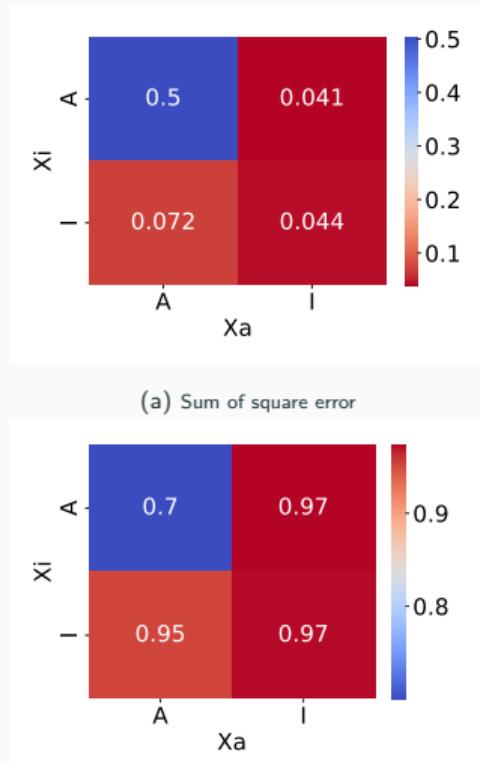


Figure 9: Full reactivation

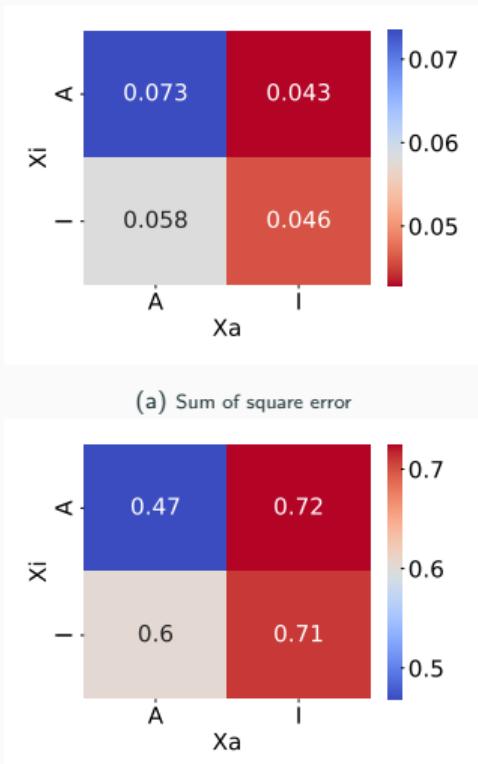


Figure 10: Partial reactivation

Testing cross connections w/ fixed self-inhibition

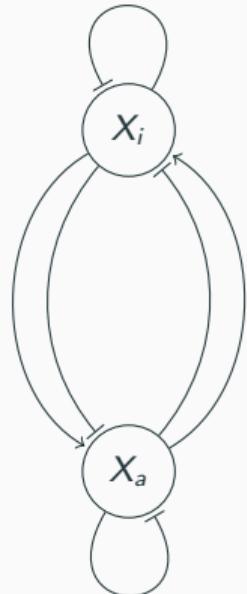


Figure 11: Cross connections

Testing cross connections w/ fixed self-inhibition

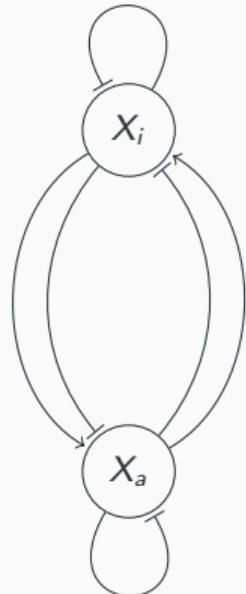
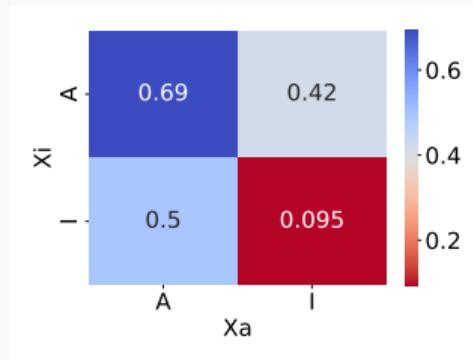
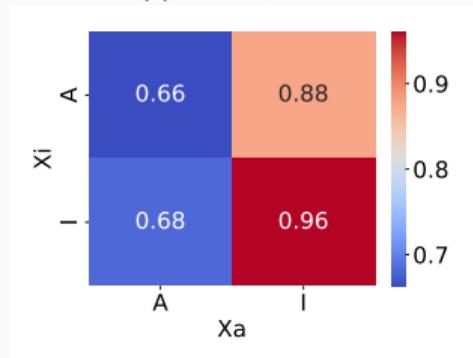


Figure 11: Cross connections



(a) Sum of square error



(b) R^2 values

Figure 12: Full reactivation

Testing cross connections w/ fixed self-inhibition

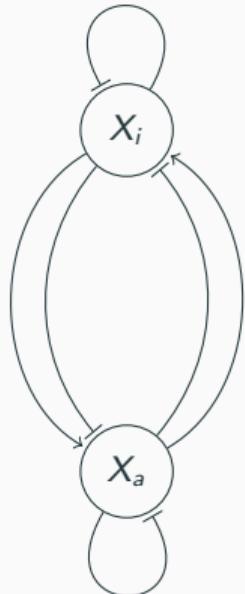
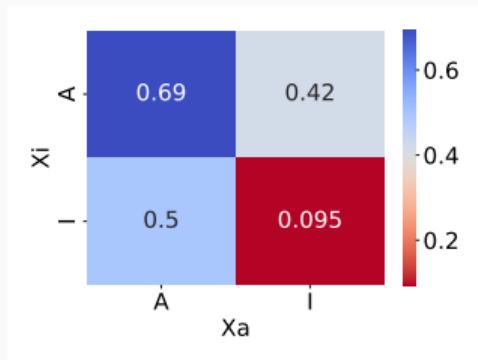
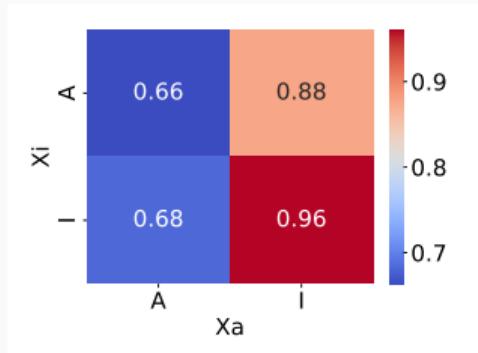


Figure 11: Cross connections

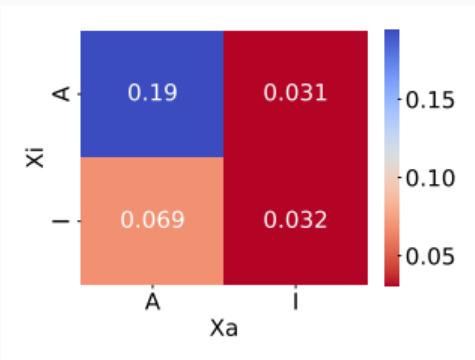


(a) Sum of square error

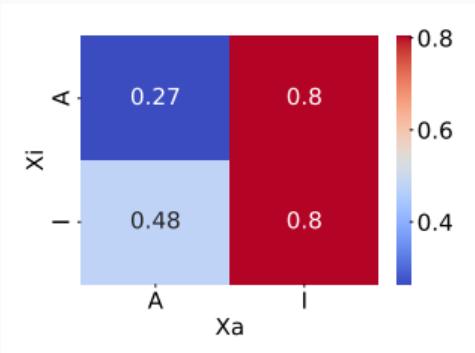


(b) R^2 values

Figure 12: Full reactivation



(a) Sum of square error



(b) R^2 values

Figure 13: Partial reactivation

Testing self connections w/ fixed cross-inhibition

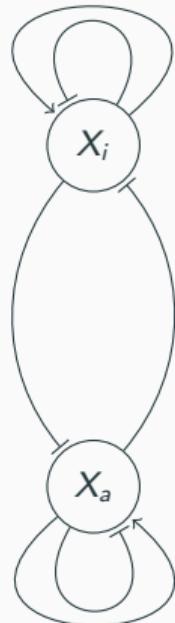


Figure 14: Self Activation

Testing self connections w/ fixed cross-inhibition



Figure 14: Self Activation

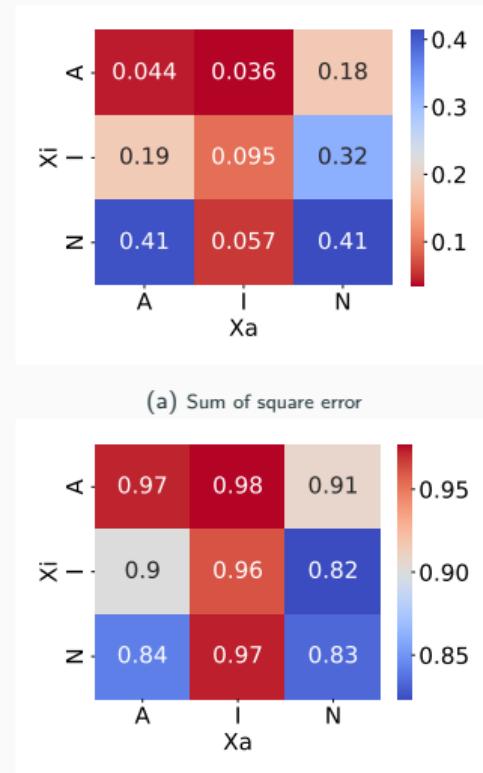
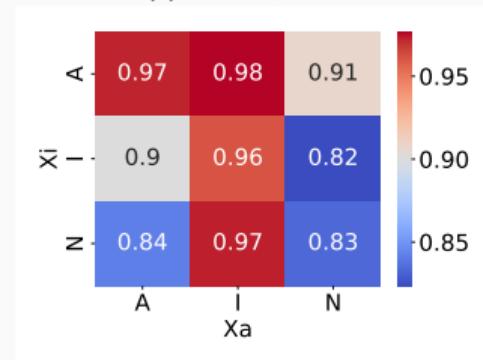


Figure 15: Full reactivation



Testing self connections w/ fixed cross-inhibition



Figure 14: Self Activation

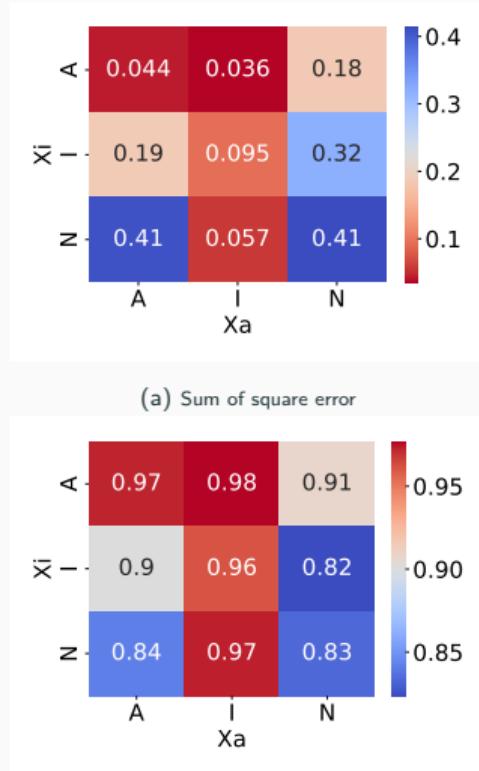


Figure 15: Full reactivation

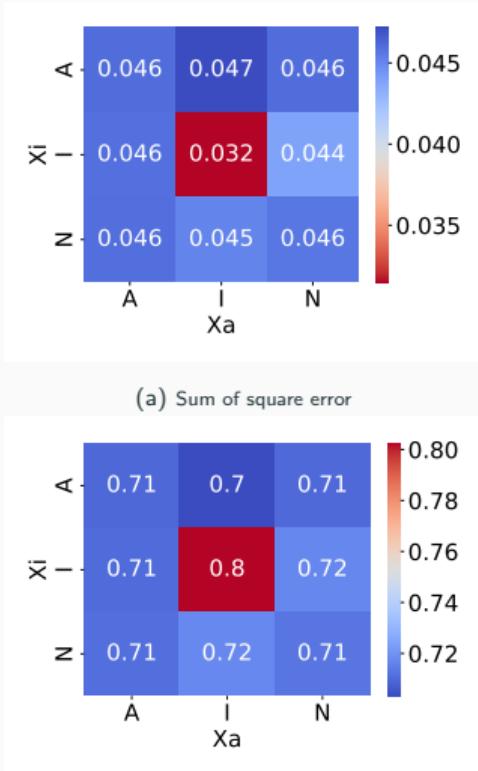
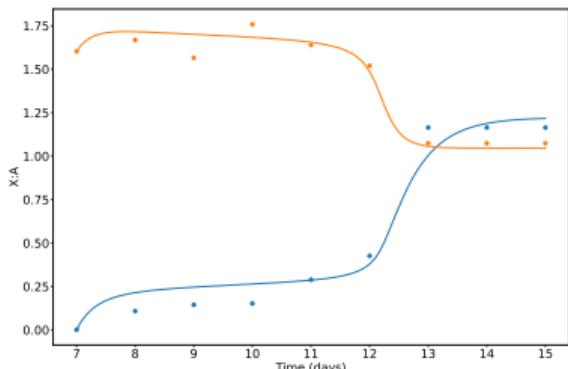
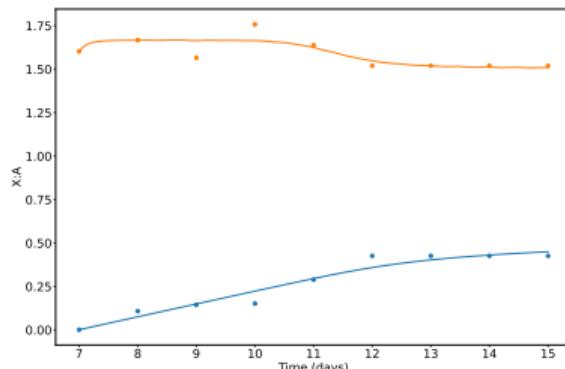


Figure 16: Partial reactivation

Complete vs Partial comparison



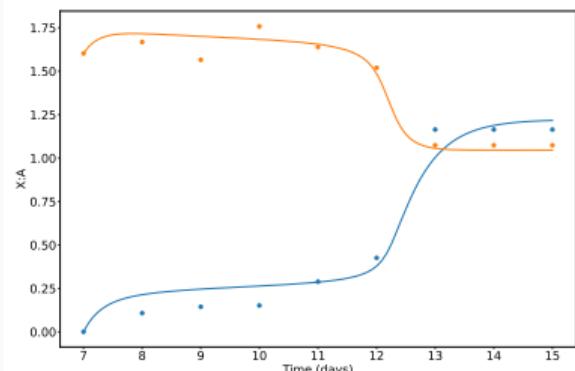
(a) Complete reactivation



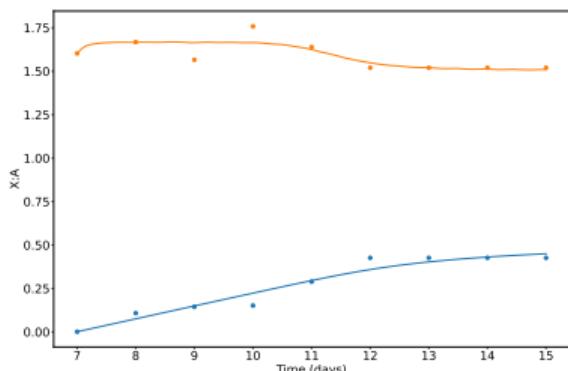
(b) Partial reactivation

Figure 17: Timeseries with fits

Complete vs Partial comparison



(a) Complete reactivation



(b) Partial reactivation

Figure 17: Timeseries with fits

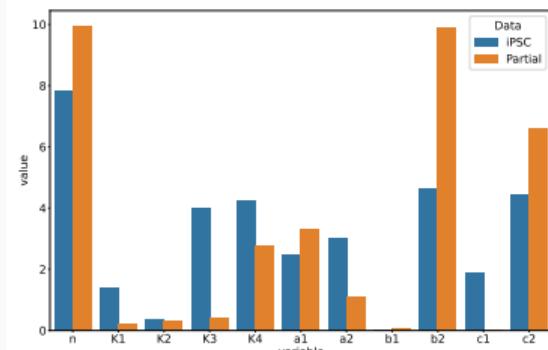


Figure 18: Parameters of fit

Conclusion

What do these mean?

- Not fully understood
- Factors present on reactivation
- Competition for factors
- Factor mediated interaction

Future plans

- Fit for primordial germ cells
 - X_i gets (hyper)activated but X_a stays upregulated
 - Sensitivity analysis

References

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