

MODELLING OF X-CHROMOSOME REACTIVATION BY TOGGLE SWITCH

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INTRODUCTION

ORIGIN OF X-CHROMOSOME INACTIVATION & UPREGULATION

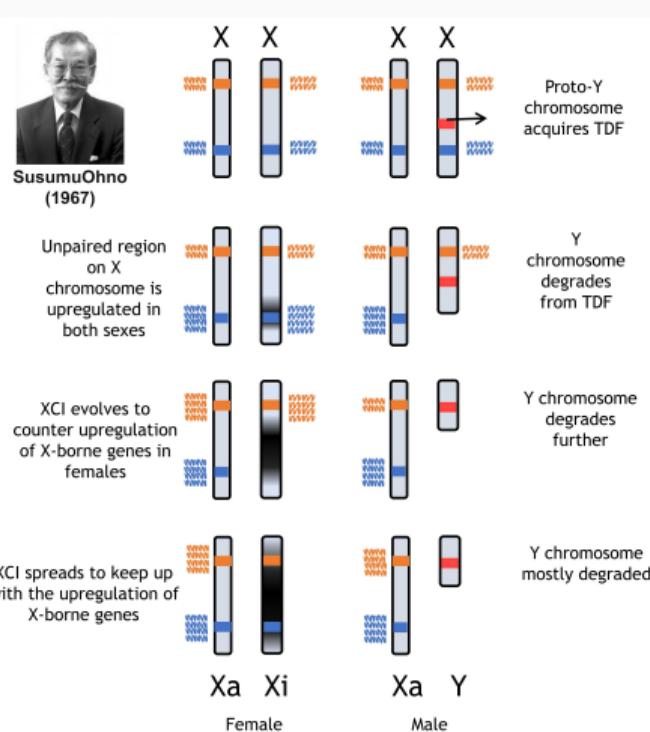


Figure 1: Ohno's hypothesis for X-Chromosome upregulation^{1 2}

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

²Credits: Srimonta Gayen

MECHANISM OF X-CHROMOSOME UPREGULATION

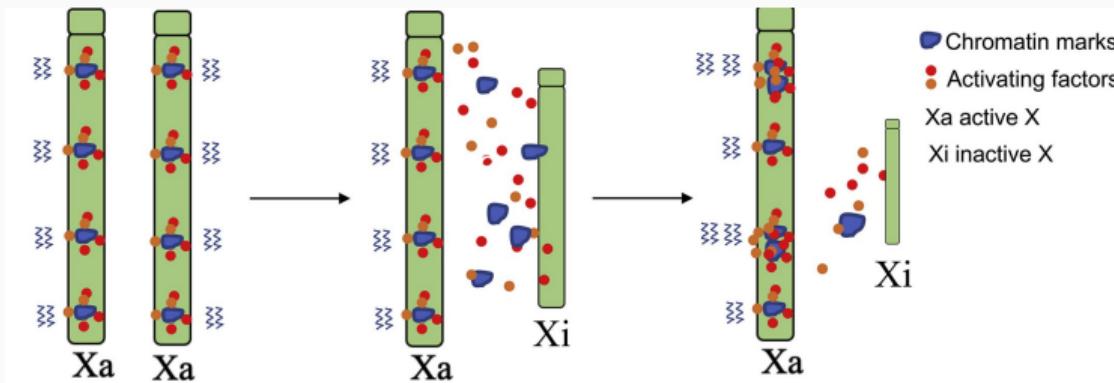


Figure 2: Model describing a mechanism of X-Chromosome upregulation^{3 4}

³ Naik et al., 2022.

⁴ Credits: Kishore Hari

OCCURANCE OF X-CHROMOSOME REACTIVATION

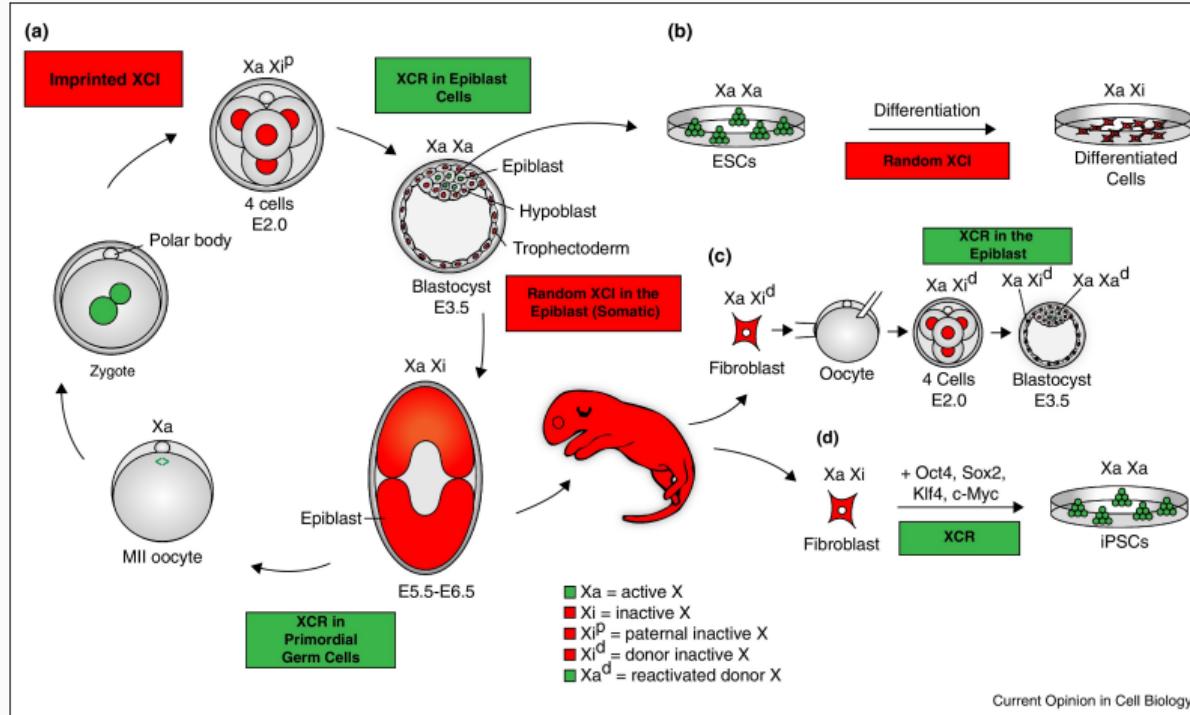


Figure 3: X-Chromosome reactivation in mouse embryo and iPSC cells^{5 6}

⁵ Pasque and Plath, 2015.

⁶ Image used from article

COMPLETE REACTIVATION OF X-CHROMOSOME

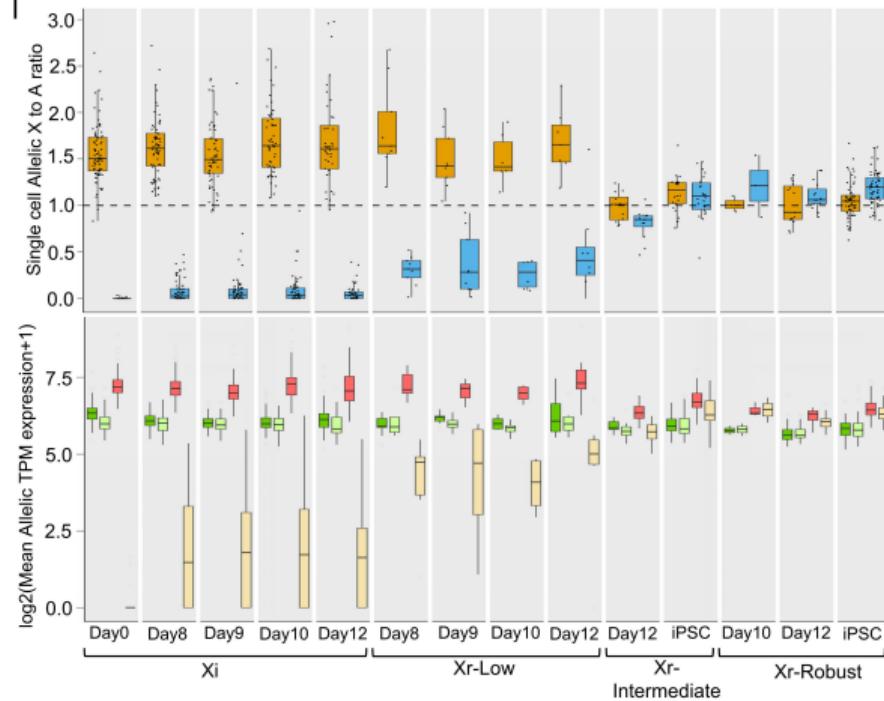


Figure 4: Erasure of X-upregulation on complete reactivation ⁷

⁷Credits: Hemant C. Naik

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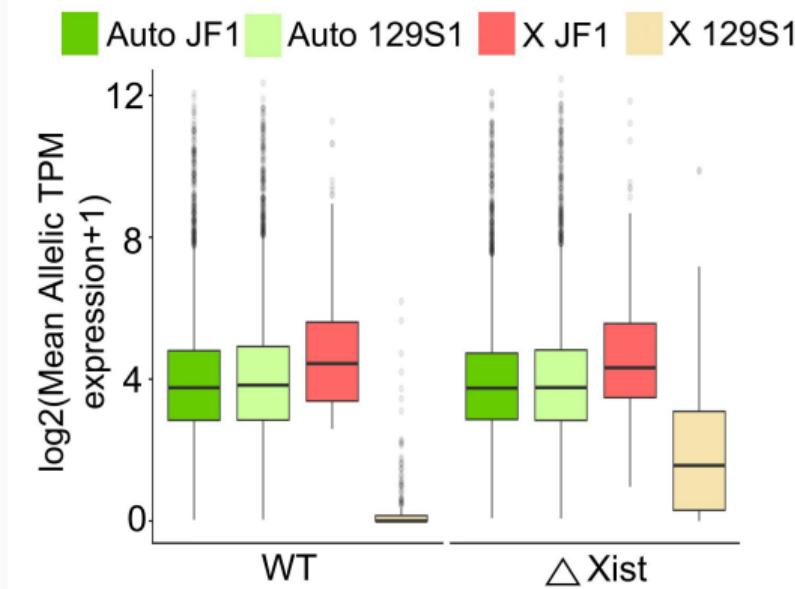


Figure 5: X-upregulation still present on partial reactivation ⁸

⁸Credits: Hemant C. Naik



- Systems biology approach
- Toggle switch = Bistability during XCI^a
- Connections influence phenotypes^b
- Simple phenomenological model

^aMutzel et al., 2019.

^bChauhan et al., 2021.

Figure 6: Mutual inhibition?

METHODS

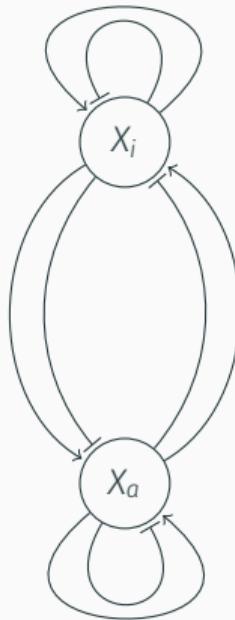
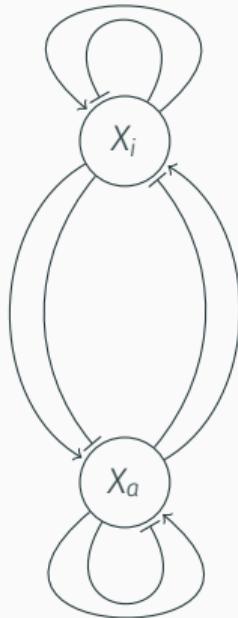


Figure 7: Possible topologies

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

Differential equations

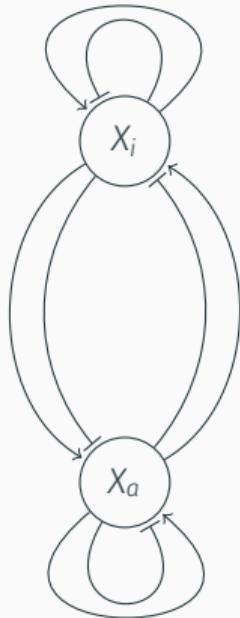


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$$f \in \{f_a, f_i, f_n\}$$

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

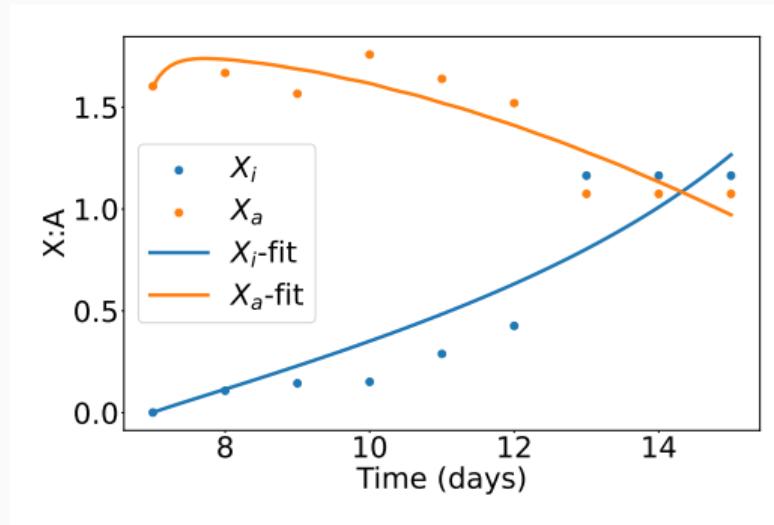
$$f_n(X, K, n) = 0 \quad (5)$$

- Differential evolution algorithm⁹
- Sample parameters with Sobol
- Solve differential equations with RK45
- Calculate sum of square error (residuals)
- Generate new parameter set
 - Mutation
 - Crossover
 - Selection
- Repeat till optimal solution

⁹Storn and Price, 1997.

RESULTS

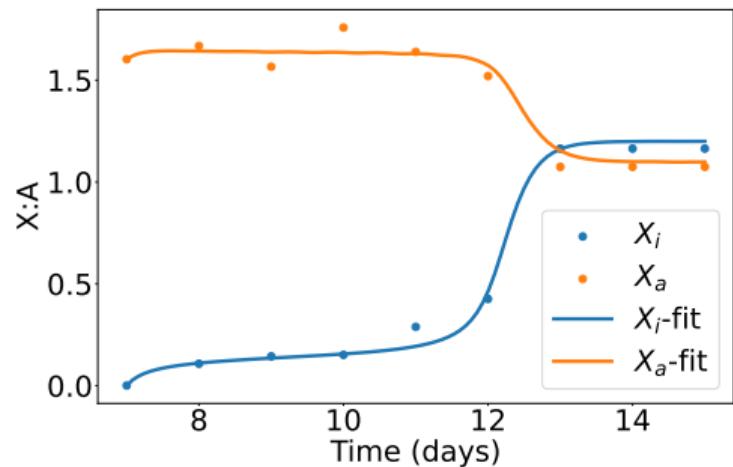
PRELIMINARY ATTEMPTS



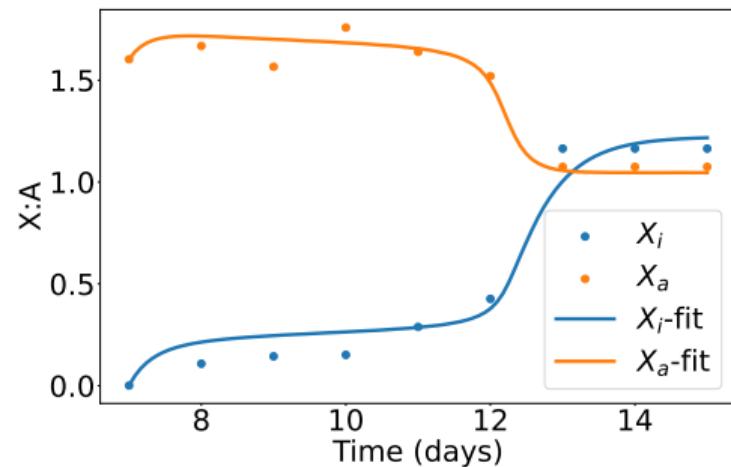
(a) Cross-inhibition

Figure 8: Fits on Full reactivation: iPSC induction data

PRELIMINARY ATTEMPTS



(b) Cross-inhibition with self-activation



(c) Cross-inhibition with self-inhibition

Figure 8: Fits on Full reactivation: iPSC induction data

TESTING SELF CONNECTIONS W/ FIXED CROSS-INHIBITION



Figure 9: Self connections

TESTING SELF CONNECTIONS W/ FIXED CROSS-INHIBITION

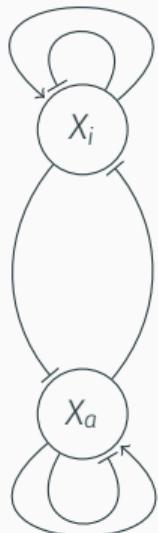
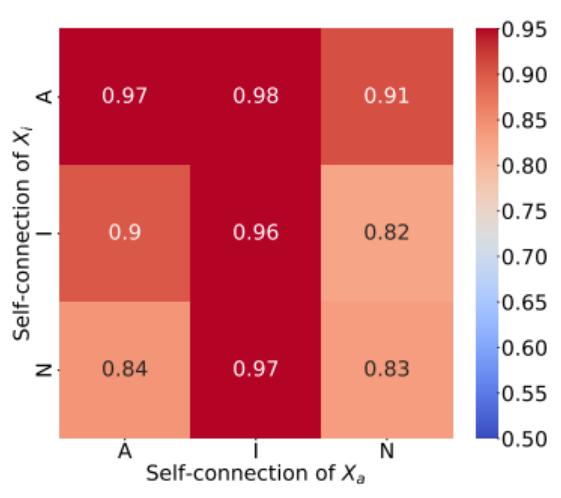


Figure 9: Self connections



(a) Full reactivation

Figure 10: Heatmaps of R^2 values

TESTING SELF CONNECTIONS W/ FIXED CROSS-INHIBITION

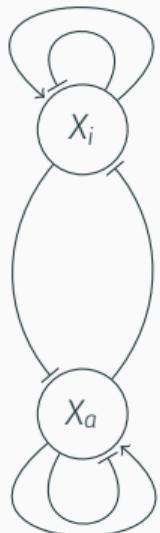
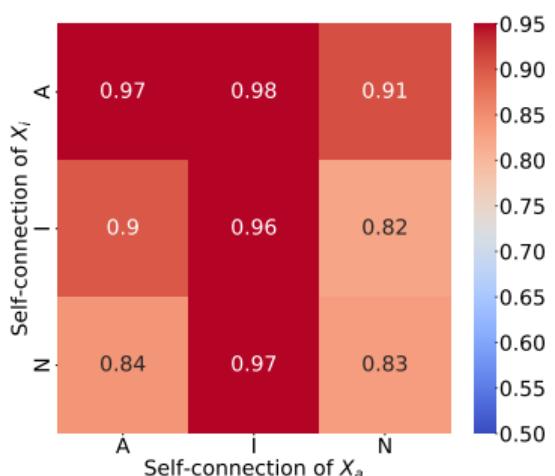
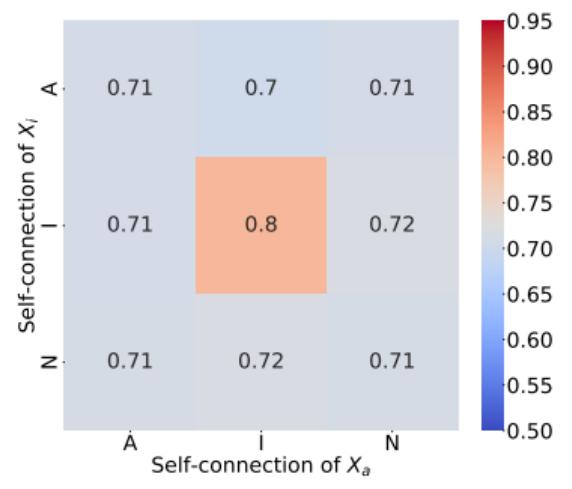


Figure 9: Self connections



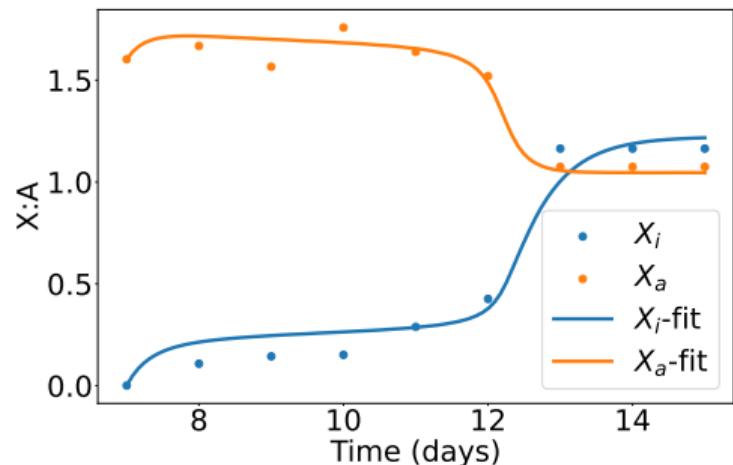
(a) Full reactivation



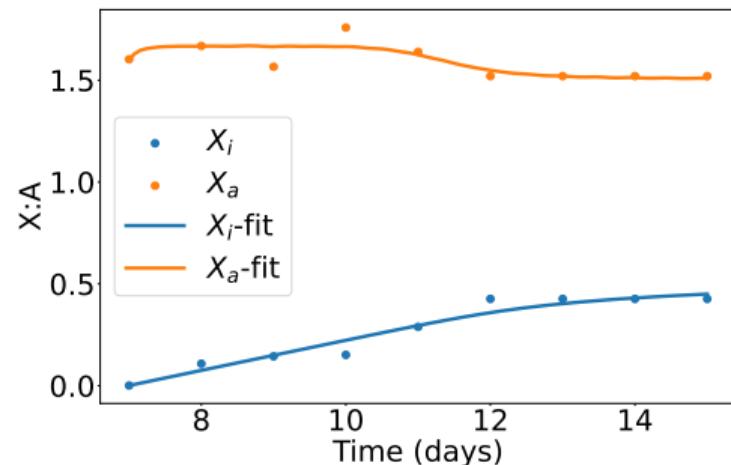
(b) Partial reactivation

Figure 10: Heatmaps of R^2 values

PLOTS OF TIMESERIES WITH FITS



(a) Complete reactivation



(b) Partial reactivation

Figure 11: Timeseries with fits of cross-inhibition with self-inhibition

TESTING CROSS CONNECTIONS W/ FIXED SELF-INHIBITION

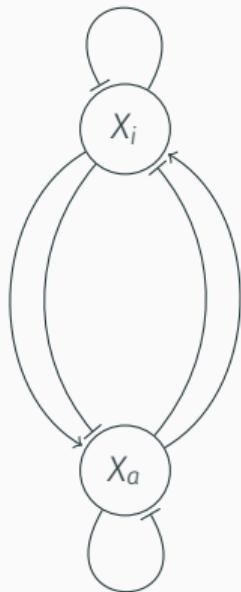


Figure 12: Cross connections

TESTING CROSS CONNECTIONS W/ FIXED SELF-INHIBITION

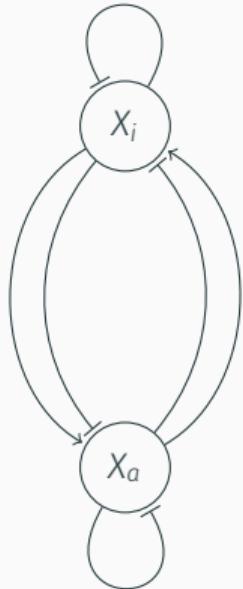
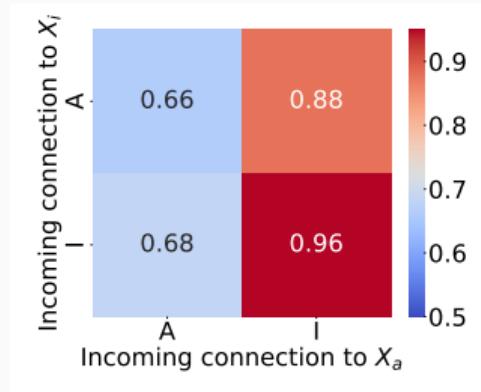


Figure 12: Cross connections



(a) Full reactivation

Figure 13: Heatmaps of R^2 values

TESTING CROSS CONNECTIONS W/ FIXED SELF-INHIBITION

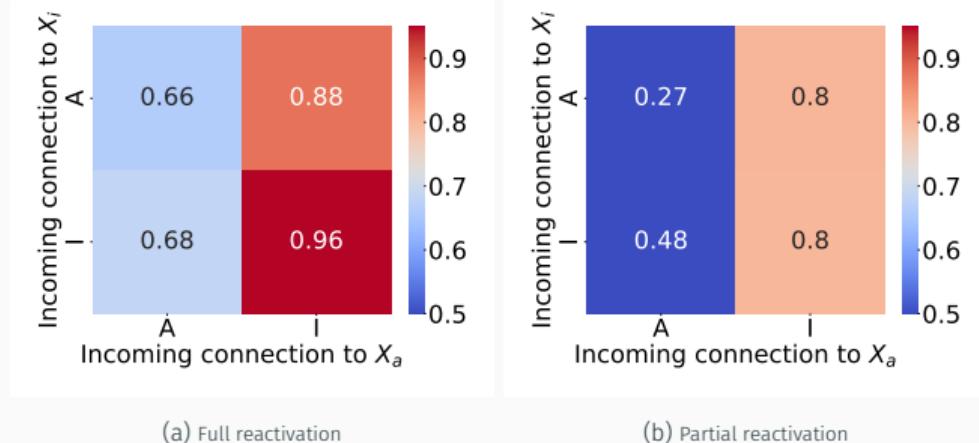
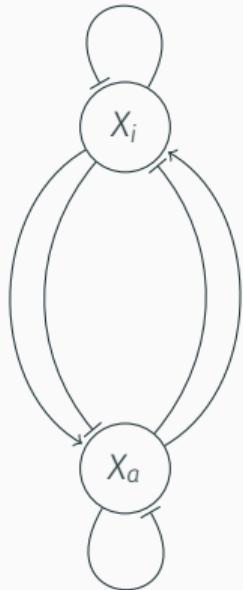


Figure 13: Heatmaps of R^2 values

Figure 12: Cross connections

TESTING CROSS CONNECTIONS W/ FIXED SELF-ACTIVATION

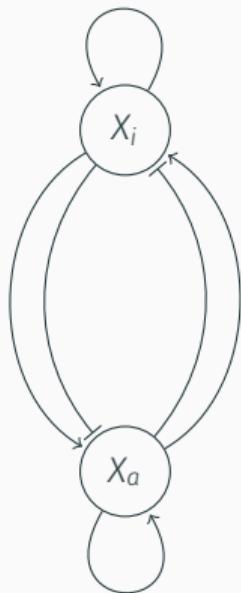


Figure 14: Cross connections

TESTING CROSS CONNECTIONS W/ FIXED SELF-ACTIVATION

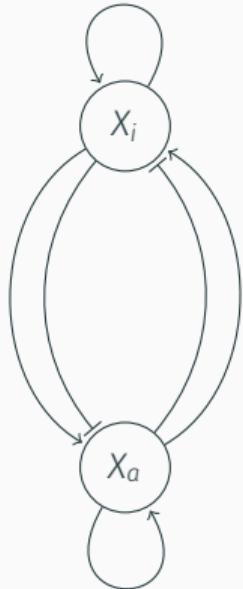
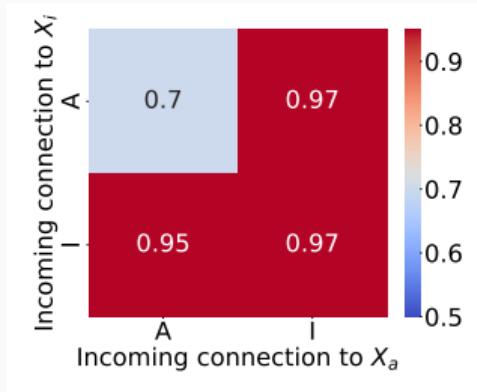


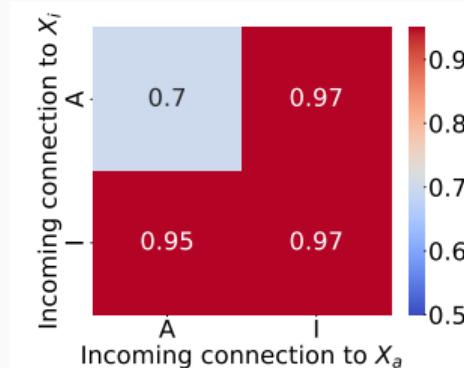
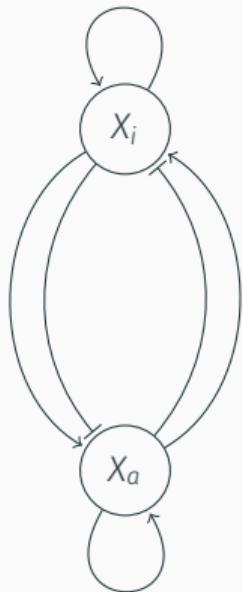
Figure 14: Cross connections



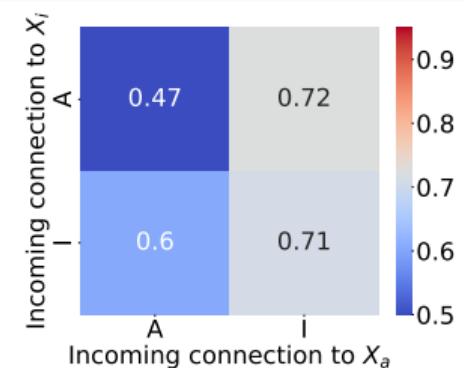
(a) Full reactivation

Figure 15: Heatmaps of R^2 values

TESTING CROSS CONNECTIONS W/ FIXED SELF-ACTIVATION



(a) Full reactivation



(b) Partial reactivation

Figure 15: Heatmaps of R^2 values

Figure 14: Cross connections

UNIVERSAL SET

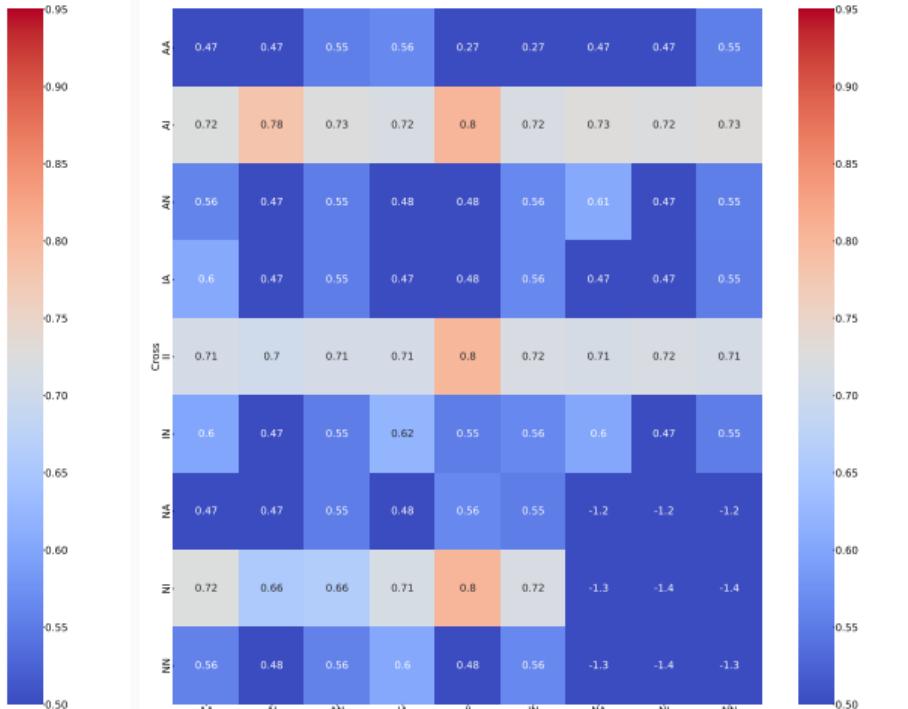
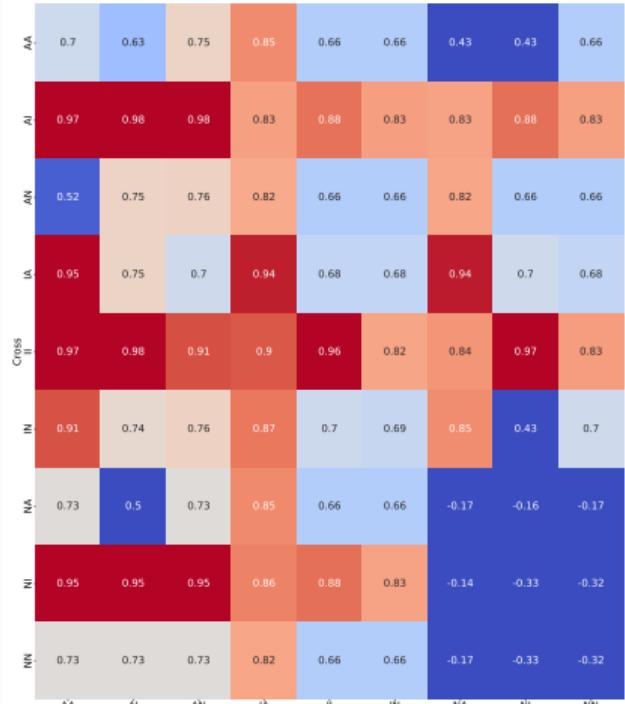


Figure 16: Heatmap of all topologies

COMPLETE VS PARTIAL COMPARISON

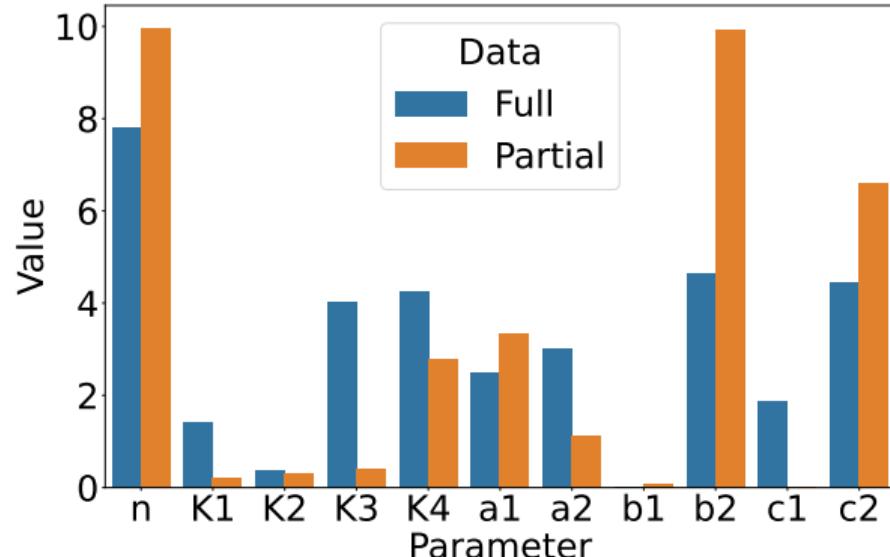


Figure 17: Parameters of fit

- cross-inhibition on $X_i \downarrow$
- cross-inhibition on $X_a \uparrow$
- self-inhibition on $X_i \approx 0$
- self-inhibition on $X_a \downarrow$

ADDITION OF NOISE

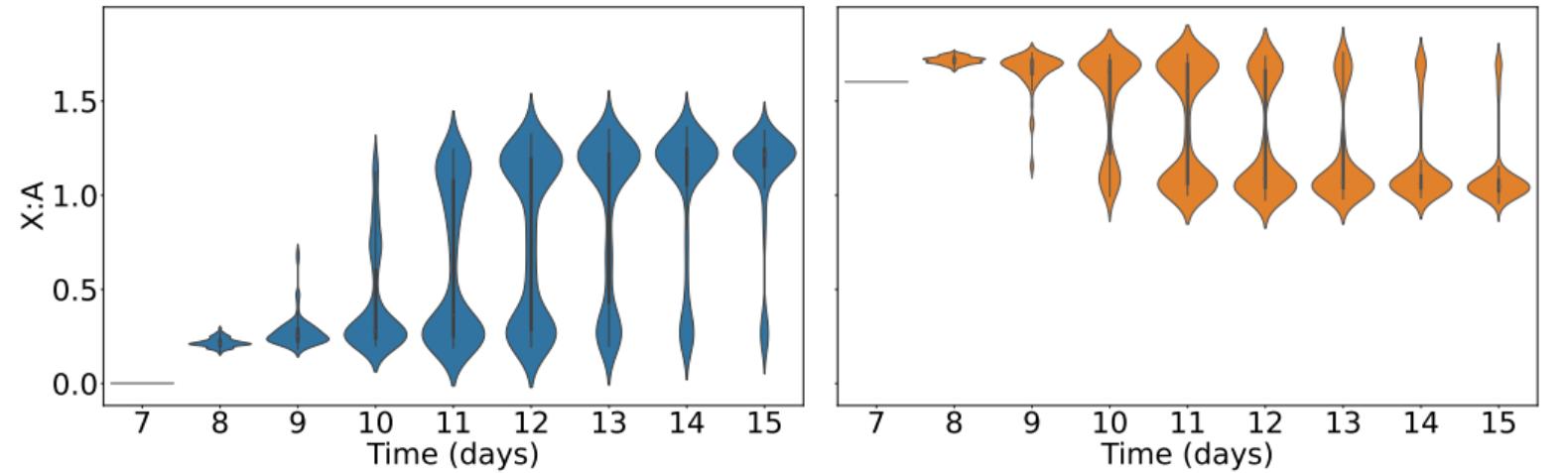


Figure 18: Reactivation with added noise

CONCLUSION

- Explains the reactivation dynamics

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- Explain heterogeneity at timepoint (X_a, X_i vs X_a, X_r)

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- What do these mean?
 - Mechanism not fully understood

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- Explain heterogeneity at timepoint (X_a, X_i vs X_a, X_r)
- What do these mean?
 - Mechanism not fully understood
 - Competition for factors
 - Factor mediated interaction

- Time series fits for more complicated topologies with more players?

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