

MARKOVIAN MODELLING OF ALLELIC COORDINATION OF TRANSCRIPTIONAL BURSTING

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IISc Bangalore

INTRODUCTION

WHAT ARE ALLELES?

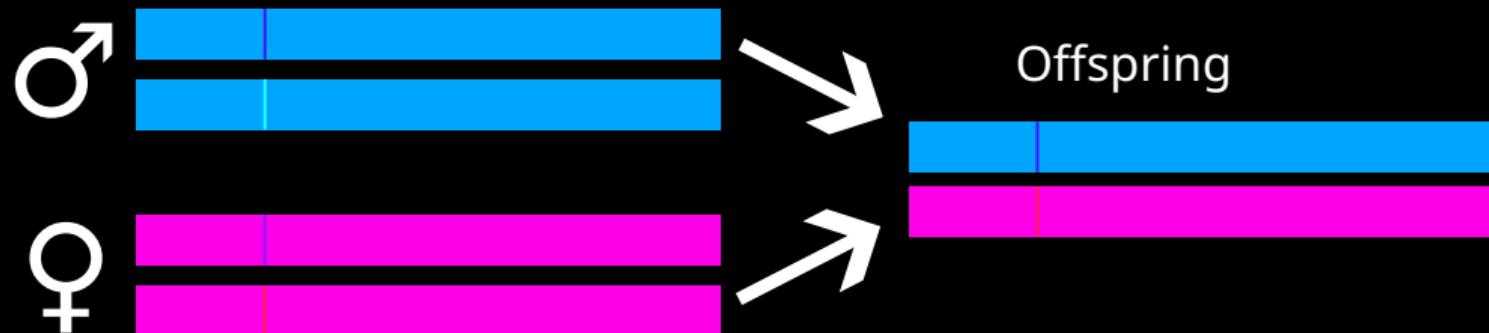


Figure 1: Schematic figure of Allele

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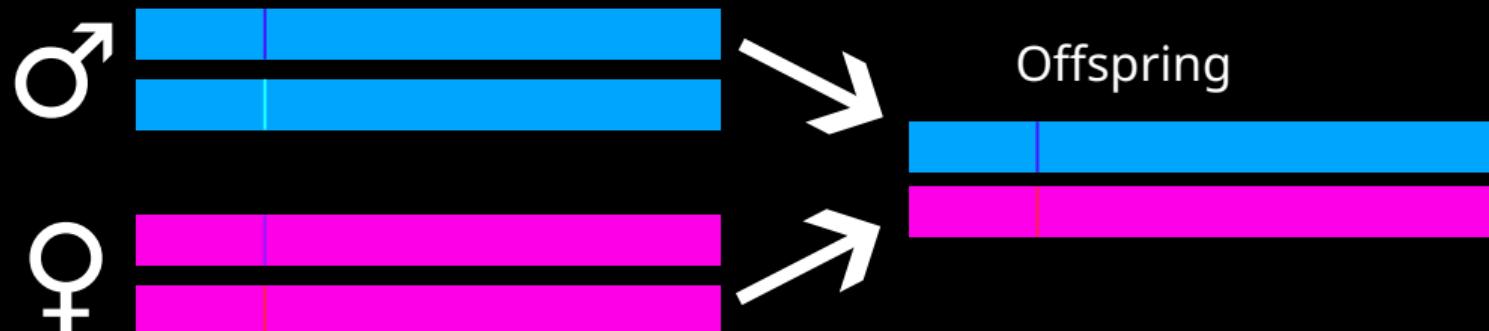


Figure 1: Schematic figure of Allele

Copies of the same gene on two chromosomes

HOW DO THE ALLELES EXPRESS?

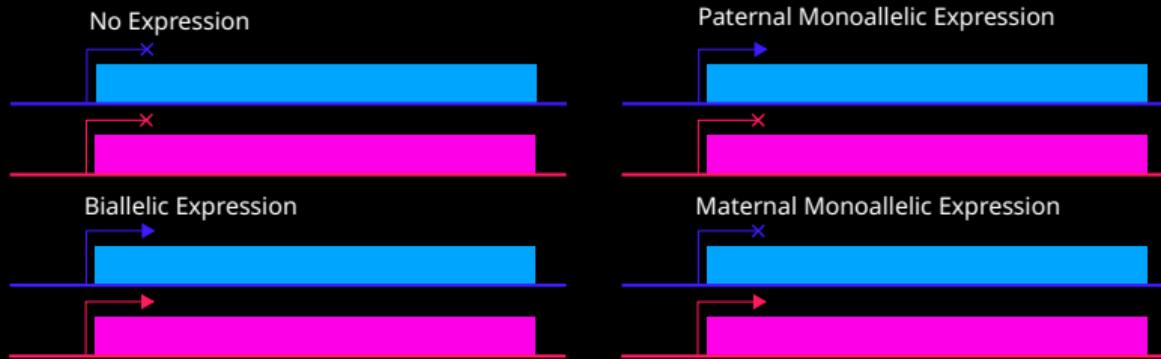


Figure 2: Allelic expression types

¹Singer-Sam, 2010.

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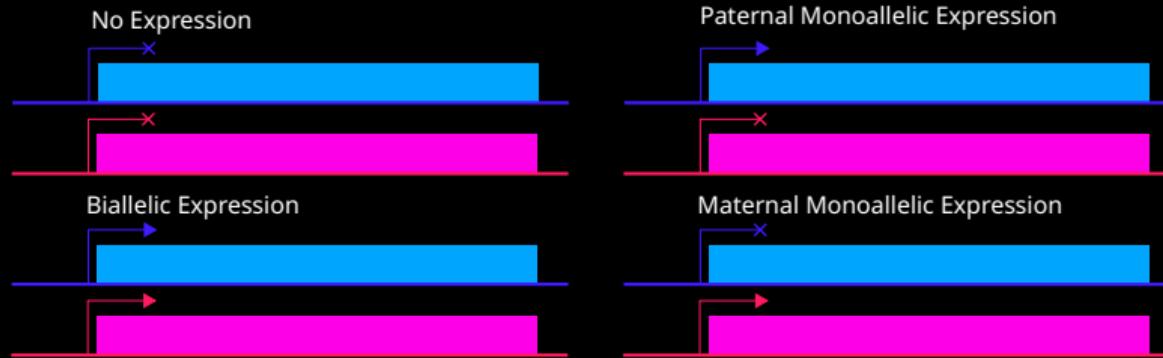


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- Imprinted vs Random

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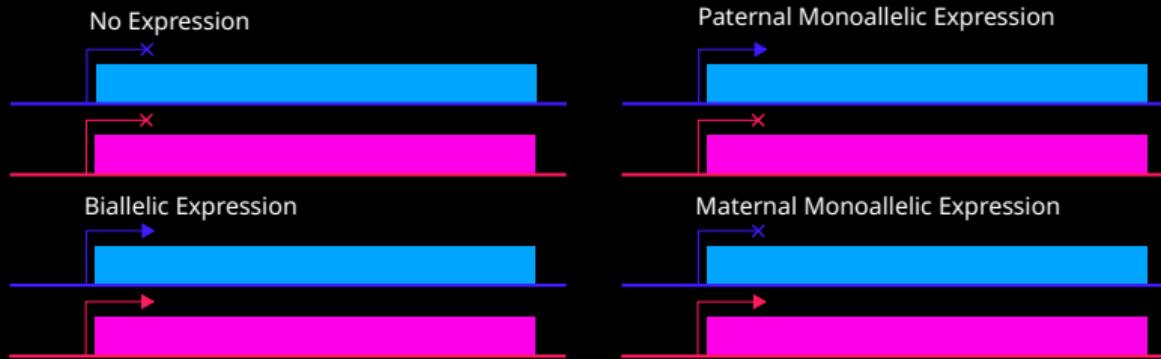


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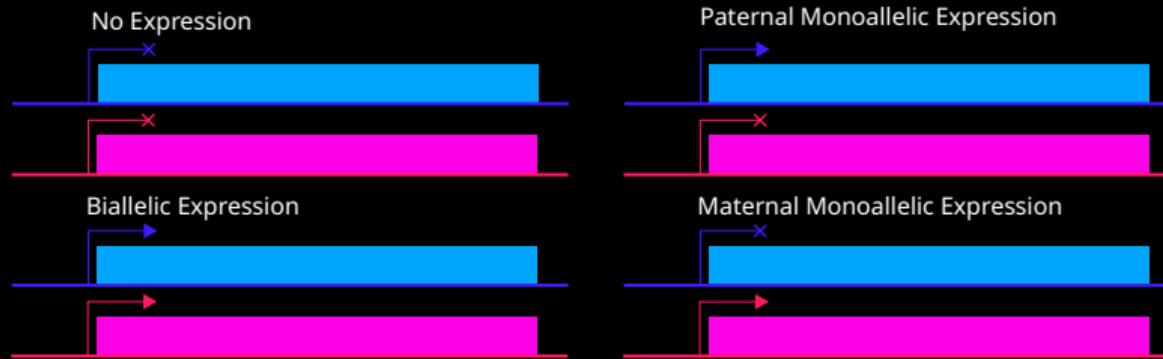


Figure 2: Allelic expression types

- Imprinted vs Random
- Fixed vs Dynamic ← Stochastic bursting

1

¹Singer-Sam, 2010.

HOW TO COORDINATE?

- p_0 = probability of both alleles off
- p_2 = probability of both alleles on

²Naik et al., 2021.

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- Fully coordinated - both off \longleftrightarrow both on

$$p_0 + p_2 = 1$$

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HOW TO COORDINATE?

- p_0 = probability of both alleles off
- p_2 = probability of both alleles on
- Fully coordinated - both off \longleftrightarrow both on

$$p_0 + p_2 = 1$$

- Fully independent

p = probability of 1 gene being on

$$p_2 = p^2 \quad ; \quad p_0 = (1-p)^2$$

$$\sqrt{p_0} + \sqrt{p_2} = 1$$

2

²Naik et al., 2021.

EXISTING WORK

Alleles are semi-coordinated in developmental genes

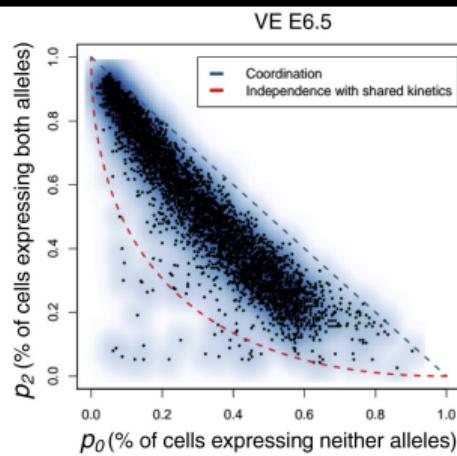
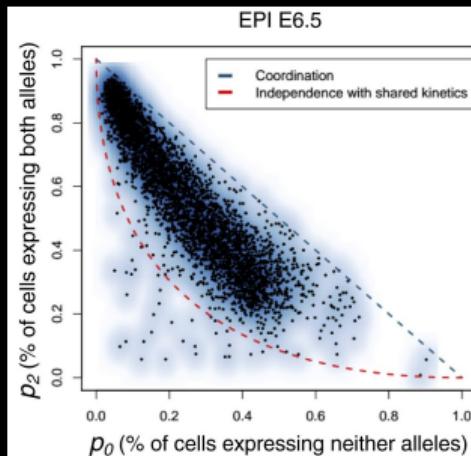


Figure 3: Experimental Data

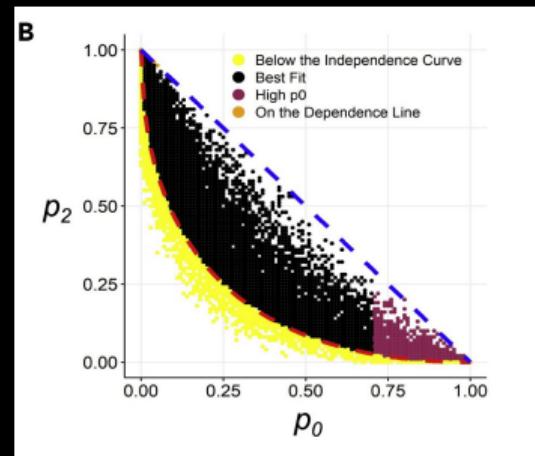


Figure 4: Kishore's Model

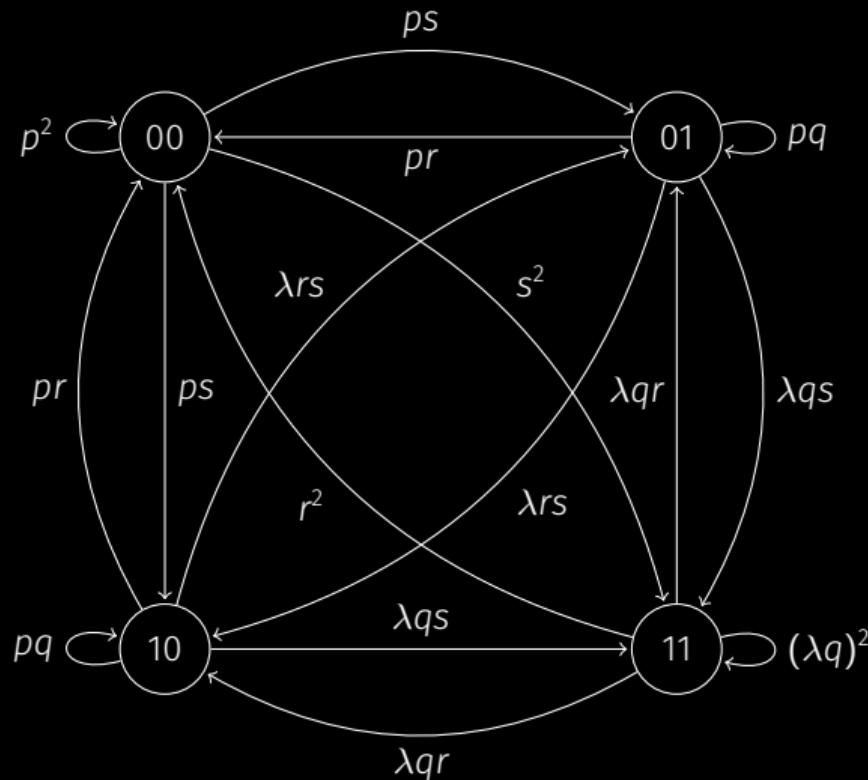
CONTEXT FOR CANCER?

- Introduces non-genetic heterogeneity
 - Switch between alleles
 - Modulate dosage levels

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 - Switch between alleles
 - Modulate dosage levels
- Coordinated bursts ← therapy resistance (Schuh et al., 2020)

MODELLING

MARKOV MODEL

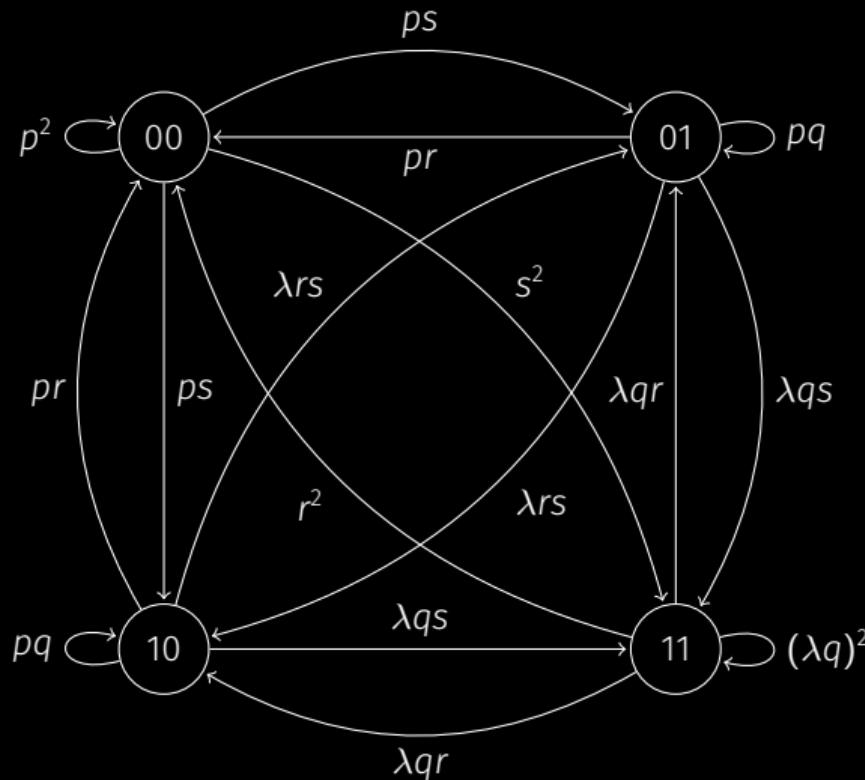


Where,

- 0 \Rightarrow Gene Off
- 1 \Rightarrow Gene On

Figure 5: Markov State Diagram

MARKOV MODEL



Where,

- 0 \Rightarrow Gene Off
- 1 \Rightarrow Gene On
- p = StayOff rate
- q = StayOn rate
- r = Off rate
- s = On rate
- λ = Interaction Parameter

Figure 5: Markov State Diagram

TRANSITION MATRIX

$$T = \begin{bmatrix} p^2 & pr & pr & r^2 \\ ps & pq & \lambda rs & \lambda qr \\ ps & \lambda rs & pq & \lambda qr \\ s^2 & \lambda qs & \lambda qs & (\lambda q)^2 \end{bmatrix}$$



Figure 6: We live in a matrix (meme)

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At steady state

$$T\vec{E} = \vec{1}\vec{E}$$



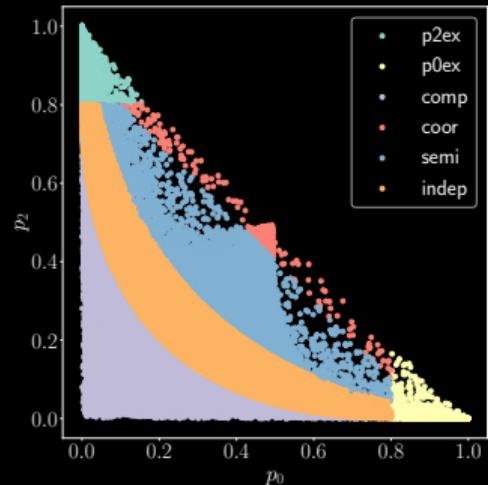
$$\vec{E} = \begin{bmatrix} p_{00} \\ p_{01} \\ p_{10} \\ p_{11} \end{bmatrix}$$

- $\sum_j T_{ij} = 1 \quad \forall i$
- $E_i \implies P(\text{state}=i)$
- $\sum_i E_i = 1$

Figure 6: We live in a matrix (meme)

PRELIMINARY RESULTS

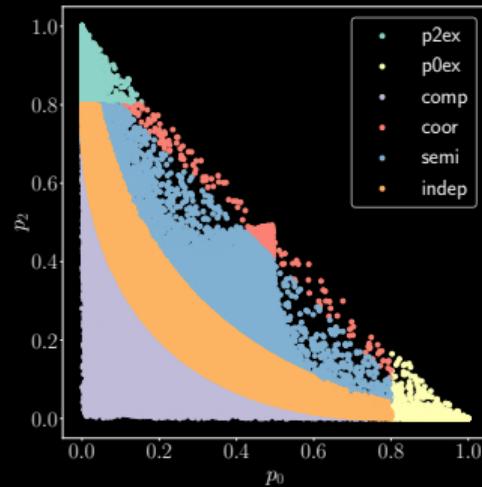
RANDOM SAMPLING



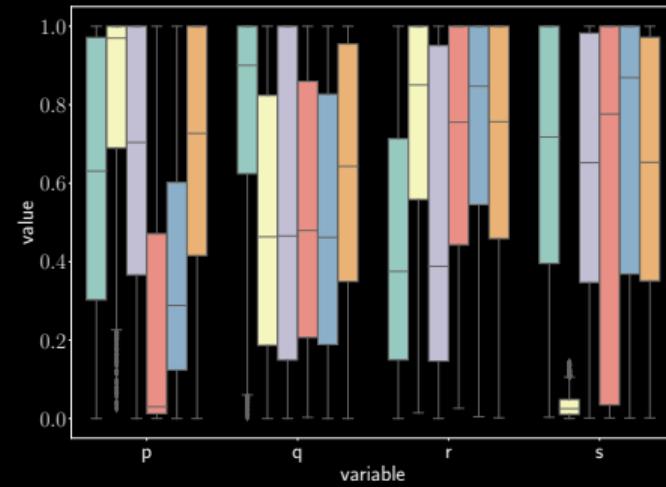
(a) p_2 vs p_0

Figure 7: $p, q, r, s \in U[0, 1]$, λ sampled log-uniformly $\in [0.01, 100]$

RANDOM SAMPLING



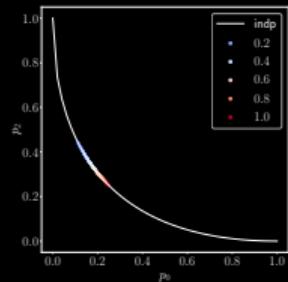
(a) p_2 vs p_0



(b) Parameters

Figure 7: $p, q, r, s \in U[0, 1]$, λ sampled log-uniformly $\in [0.01, 100]$

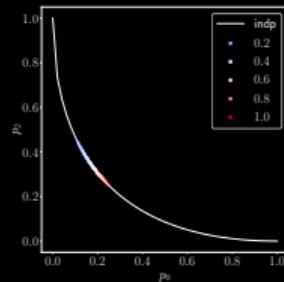
PARAMETER SWEEP



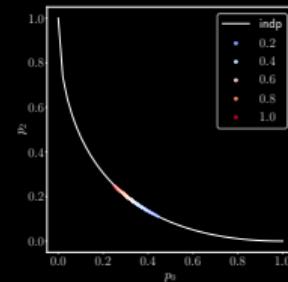
(a) p

Figure 8: Parameter sweep

PARAMETER SWEEP



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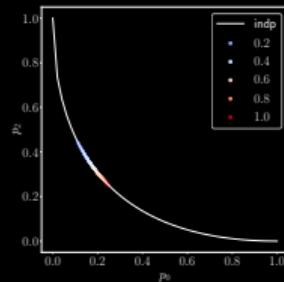


(b) q

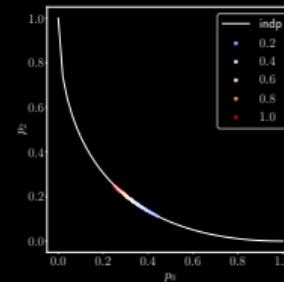
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⁴ λ labels in \log_{10}

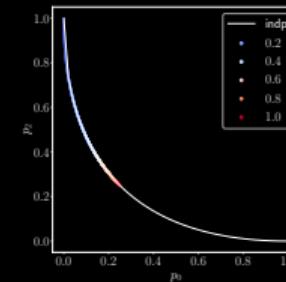
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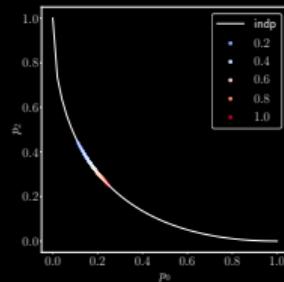
(b) q



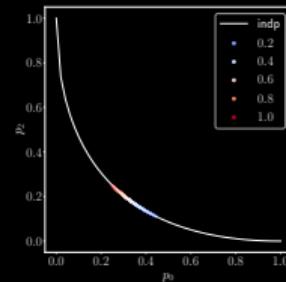
(c) r

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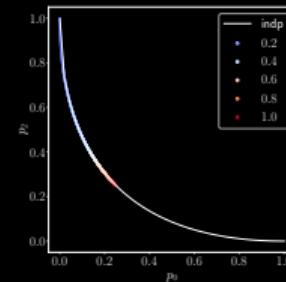
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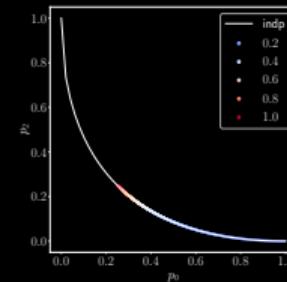
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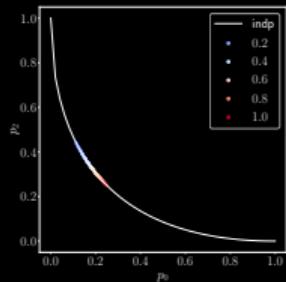
(c) r



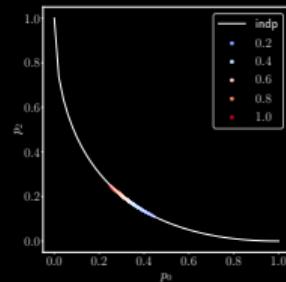
(d) s

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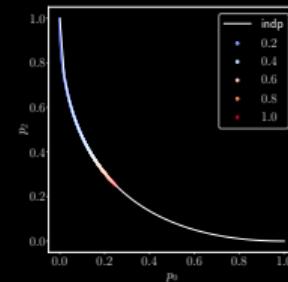
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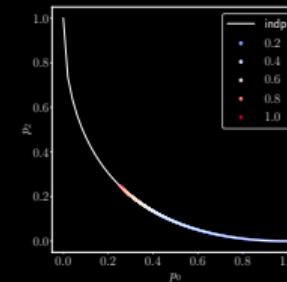
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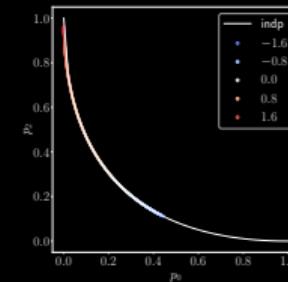
(b) q



(c) r



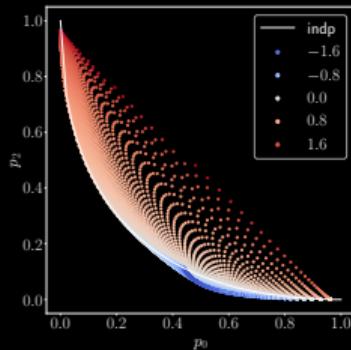
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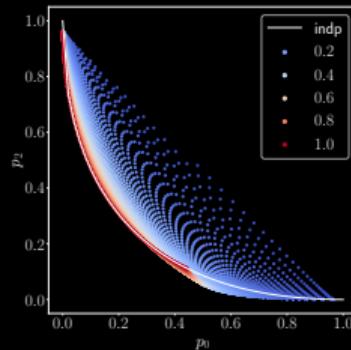
(e) λ

Figure 8: Parameter sweep

PAIRED PARAMETER SWEEP



(a) $s \& \lambda$ with λ coloured

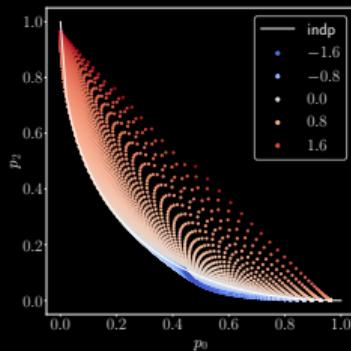


(b) $s \& \lambda$ with s coloured

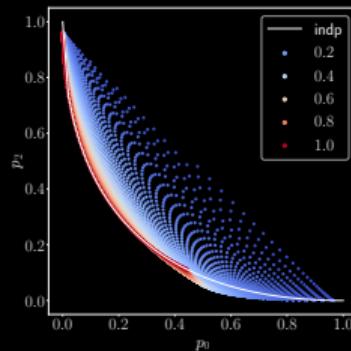
Figure 9: Parameter sweep in pairs

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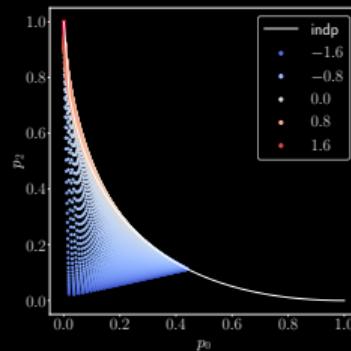
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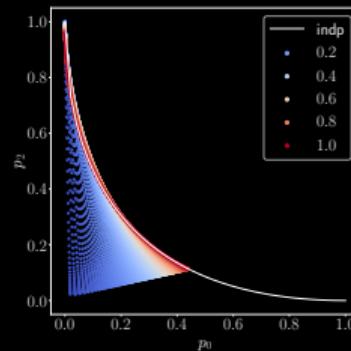
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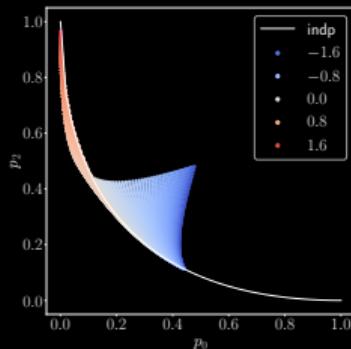
(c) $r \& \lambda$ with λ coloured



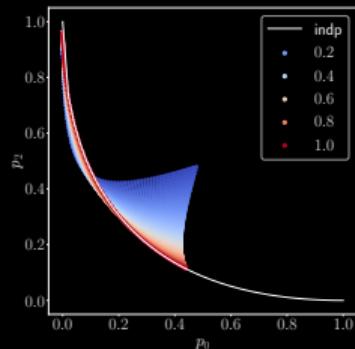
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PAIRED PARAMETER SWEEP



(a) $p\&\lambda$ with λ coloured



(b) $p\&\lambda$ with p coloured

Figure 10: Parameter sweep in pairs

PAIRED PARAMETER SWEEP

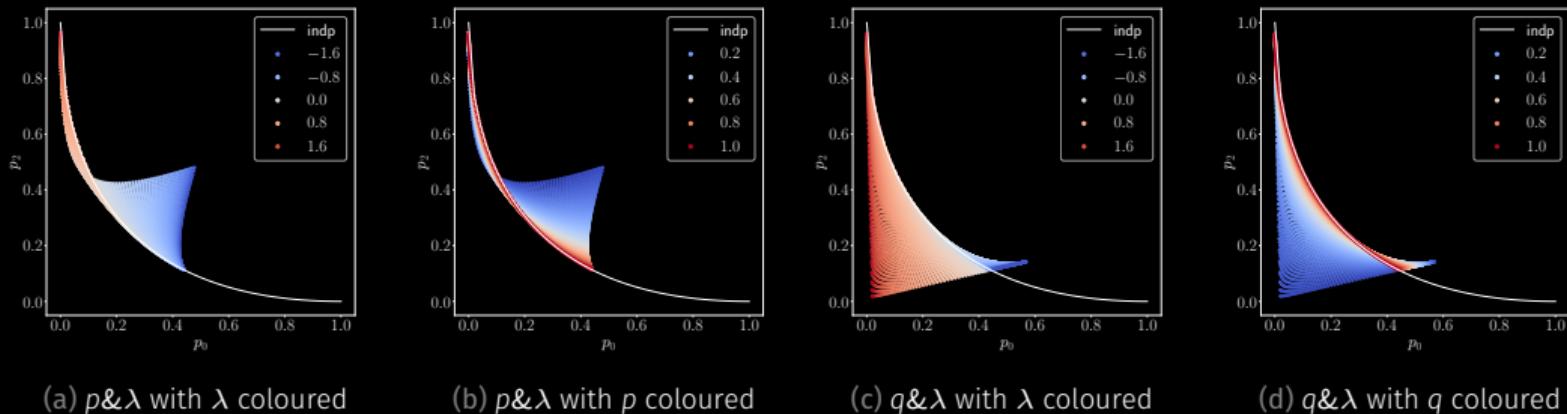


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CONCLUSIONS?

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- Not tested on cancer systems

THANK YOU
QUESTIONS, COMMENTS, FEEDBACK

REFERENCES

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