Mathematical modelling of cell cycle dynamics in glioblastoma subpopulations

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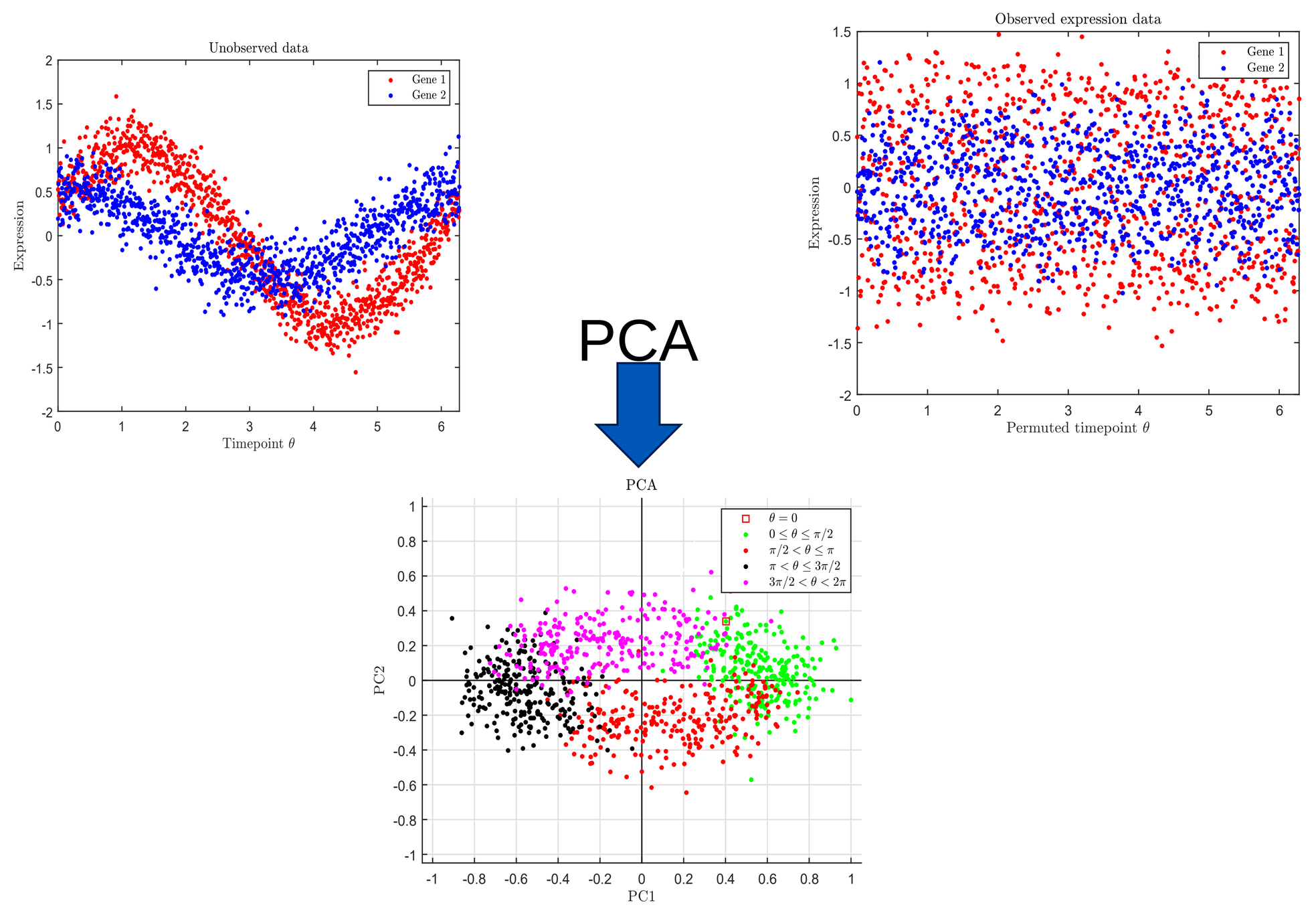
INTRODUCTION

Glioblastoma (GBM) is the most aggressive and most common primary malignant brain tumor in adults, with a poor average survival time of 15 months. One of the key challenges in successfully treating GBM is its heterogeneity, with multiple distinct cellular subtypes that have been shown to occur on both inter- and intra-patient levels. Three main classifications, classical/proliferative, mesenchymal and proneural have become commonly demonstrated phenotypes.

The cell cycle is a fundamental and highly conserved process that controls faithful division of cells; dysregulation of the cell cycle is known to be a key driver in many cancers. However, how the cell cycle is differently regulated between malignant GBM subtypes has not been well classified *in vivo.* We compare cell cycle regulation/dysregulation among these three subtypes, in a recently published single nucleus RNAseq (snRNAseq) data set[1], using Tricycle[2], an R/Bioconductor package that utilises principal component analysis and transfer learning to infer cell cycle stage (CCS) from any snRNAseq data set. We find that the proliferative GBM subtype has the highest proportion of actively dividing cells (cells in: S/G2/M phases), while both the mesenchymal and proneural subtypes have a very low proportion of actively dividing cells. This provides evidence for a proliferation-migration dichotomy between GBM subtypes.

PCA OF CYCLIC FUNCTIONS

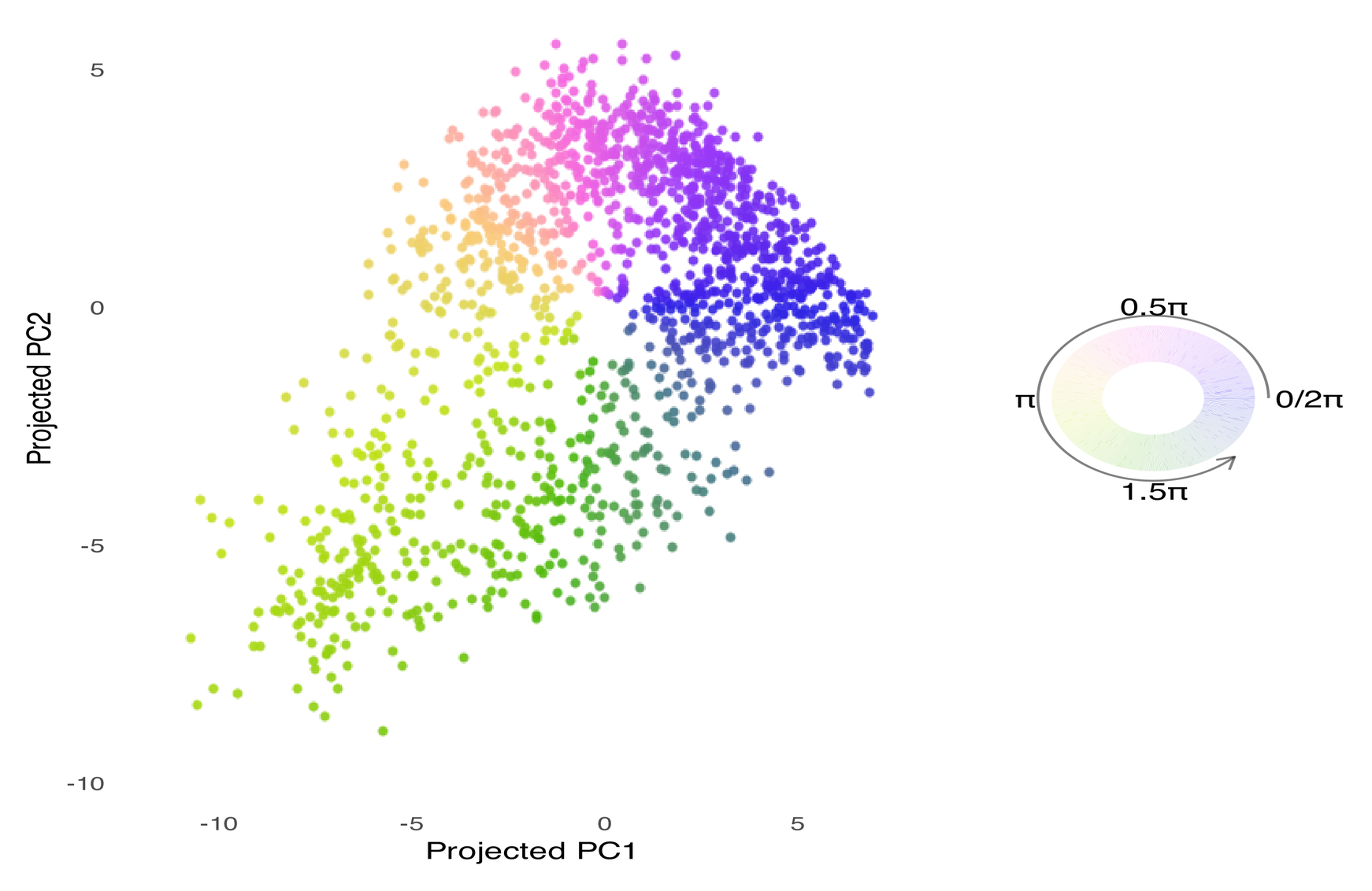
A key result that Tricycle uses to infer cell cycle position is that PCA of cyclic functions produces an ellipsoid pattern in PCA space. Below we demonstrate this with a simplified two gene system.



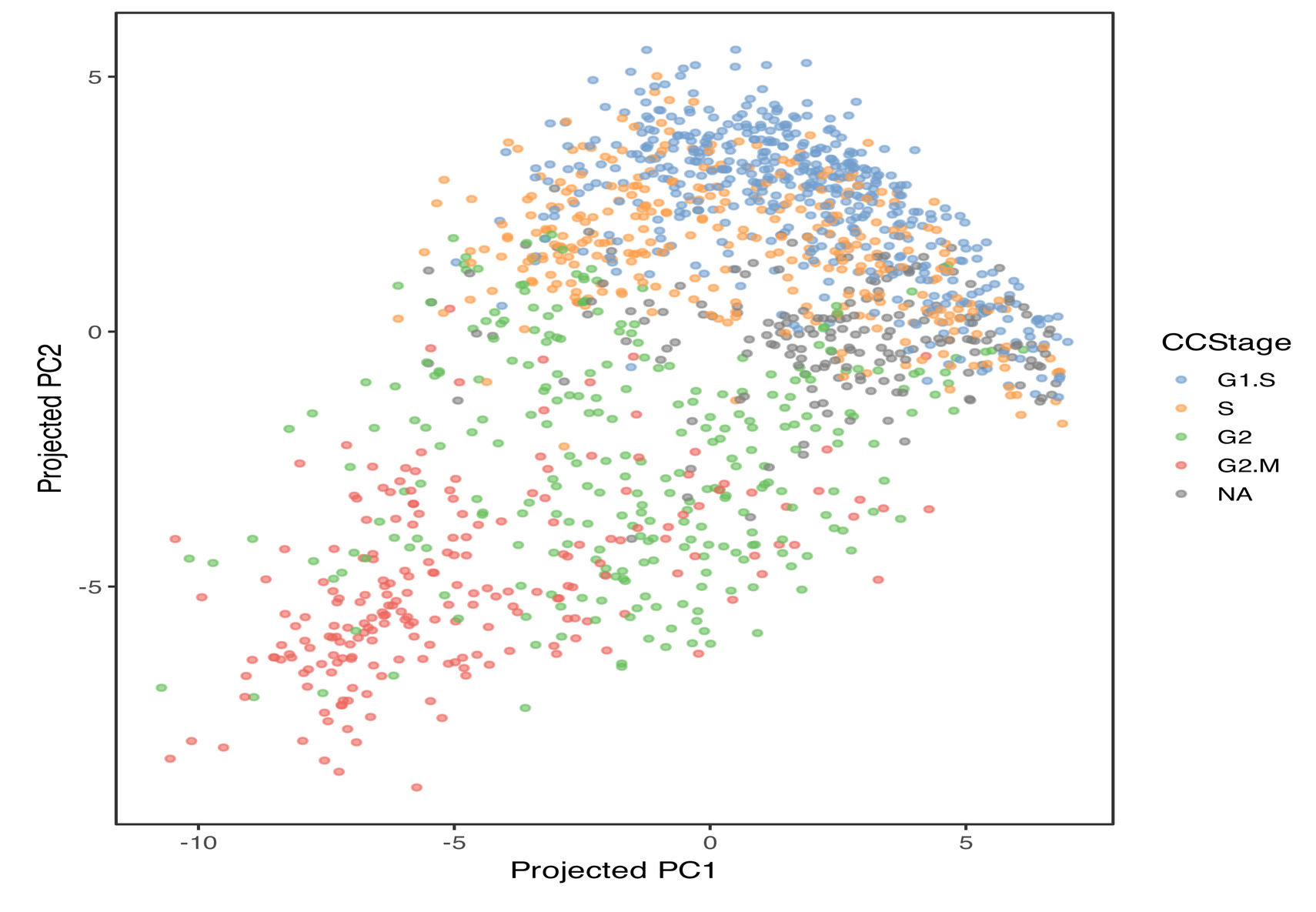
TRICYCLE RESULTS

We perform Tricycle analysis on the three main malignant GBM subtypes (gl_Pro, gl_Mes, gl_PN). Tricycle assigns cell cycle phase along a continuum from 0 to 2π, which can be related to the classical discrete cell cycle stages as: $0/2\pi \approx$ G1/G0, $0.5\pi \approx$ S, $\pi \approx$ G2, and $1.5\pi \approx$ M. We verify our results from Tricycle by also performing discrete CCS assignments using the Schwabe method[3].

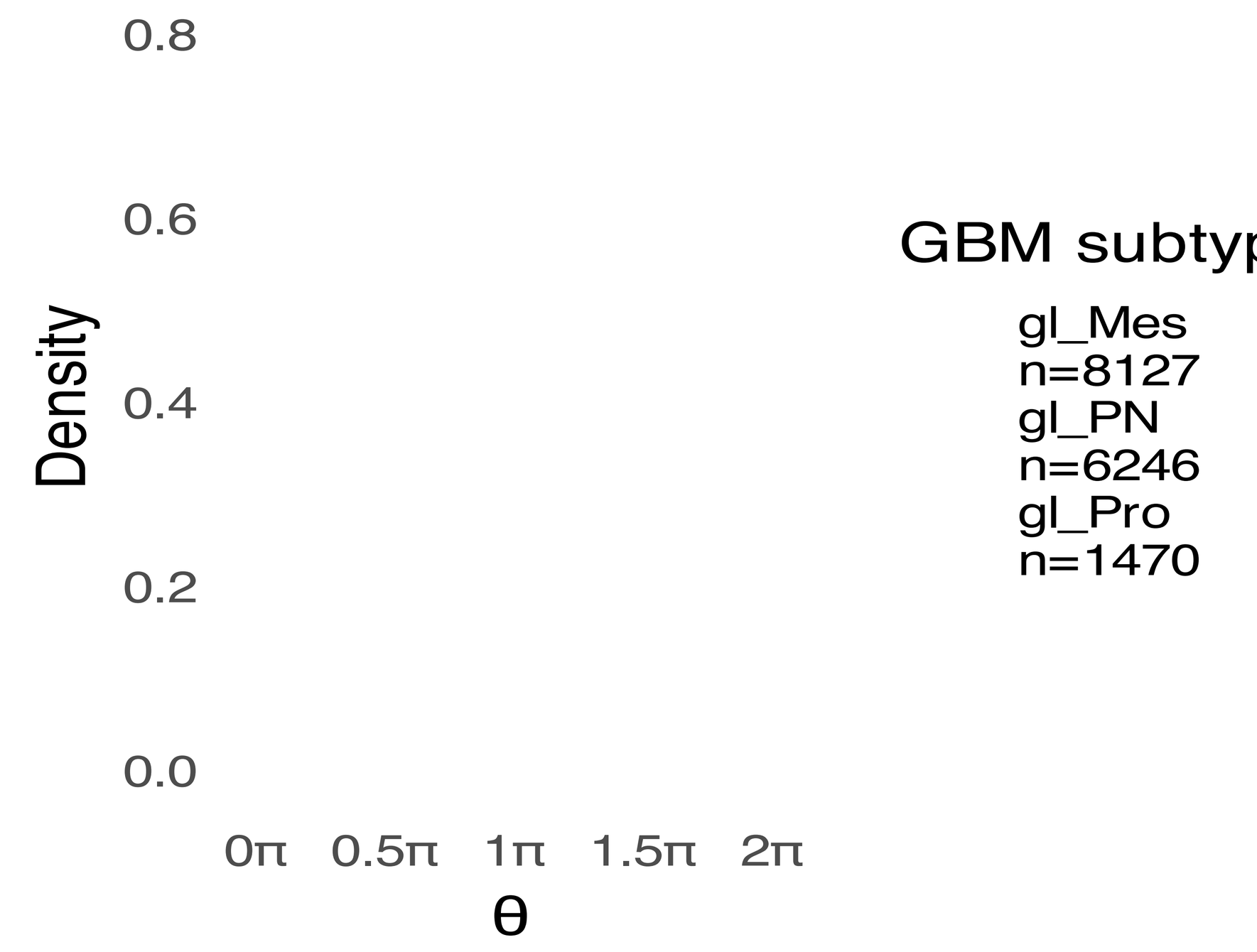
Tricycle results for gl_Pro



Schwabe[3] discrete CCS classification agrees with tricycle assignments



Density profile of phase distributions for all three GBM subtypes



MATHEMATICAL MODEL FOR CELL CYCLE

Our mathematical model for the cell cycle takes the form

$$\frac{\partial g}{\partial t} + c(t,\theta,g)\frac{\partial g}{\partial \theta} + d(t,\theta)g(t,\theta) = 0$$

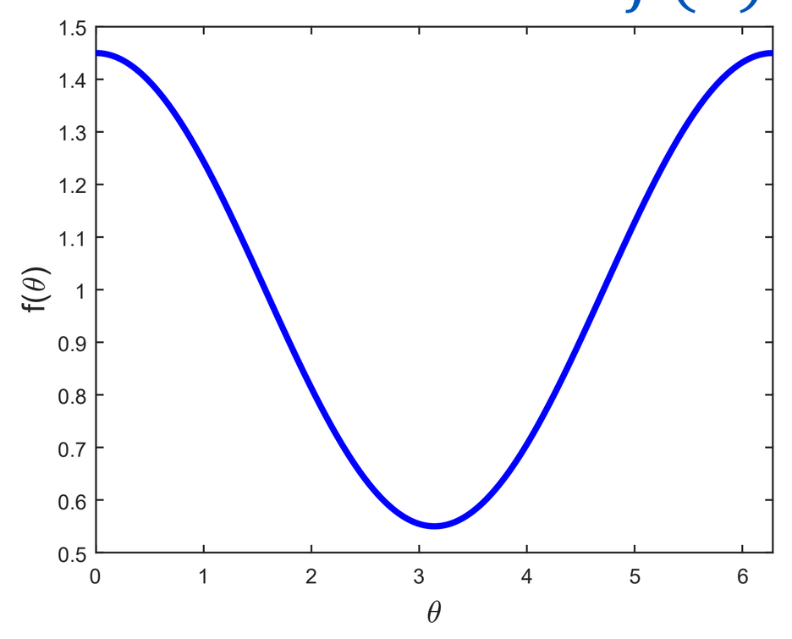
$$g(t,\theta=0) = 2\int_0^{2\pi} K(t,\hat{\theta})g(t,\hat{\theta})d\,\hat{\theta}$$

where θ represents cell cycle phase, $c(t,\theta,g)$ is the speed of progression through the cell cycle, $d(t,\theta)$ is the death rate, and $K(t,\theta)$ the mitosis rate. In the special case when, $K(t,\theta) = \delta(\theta - 2\pi)$, then via properties of the delta function the boundary condition simplifies to $g(t,\theta=0) = 2g(t,2\pi)$.

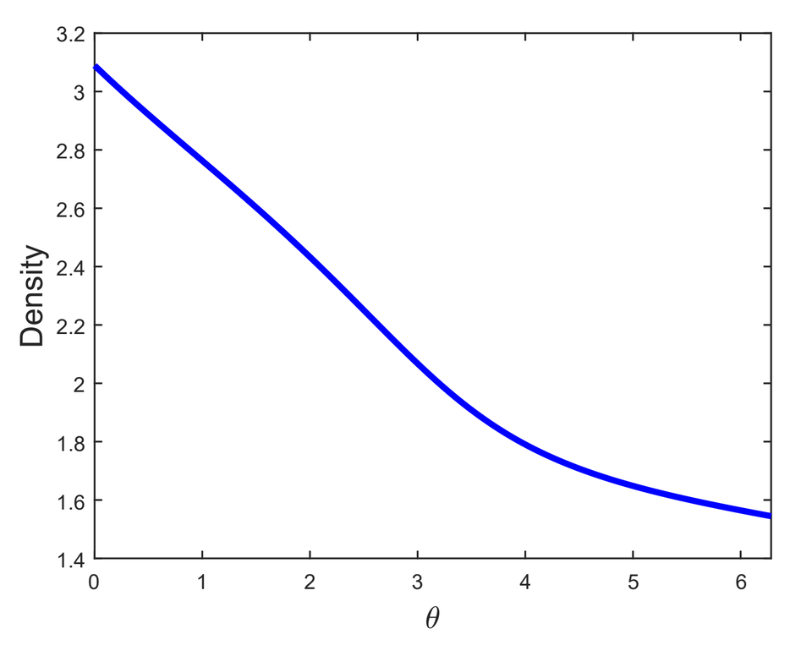
The speed of progression through the cell cycle can determine the distribution of phases at steady state. We take this speed to be given by

$$c(t,\theta,g) = \frac{a_0 + a_1 f(\theta)}{1 + \frac{g(t,\theta)}{\kappa}}$$

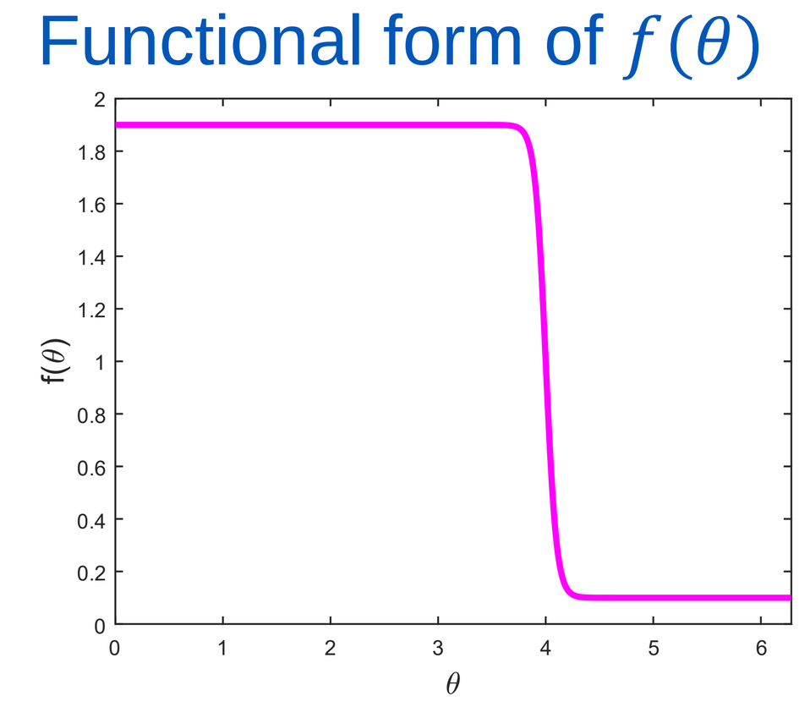
Functional form of $f(\theta)$



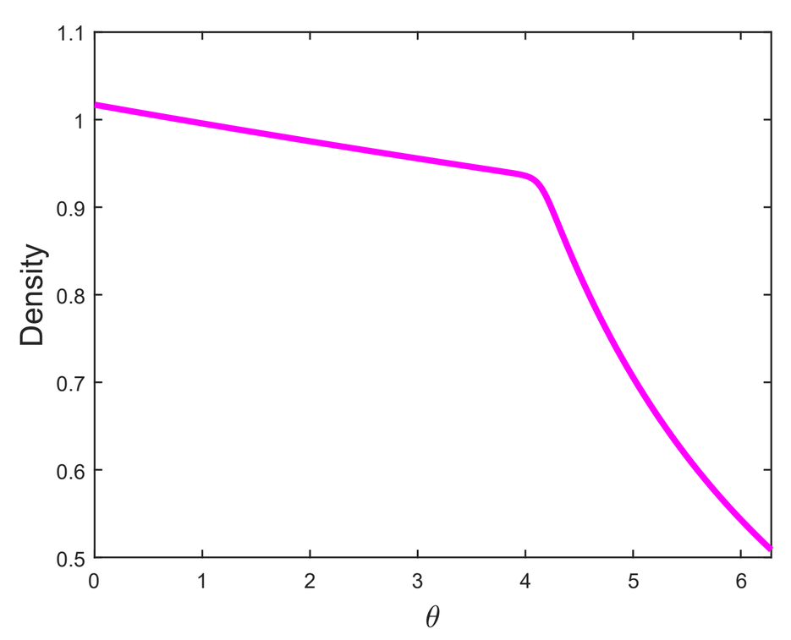
Steady state phase distribution



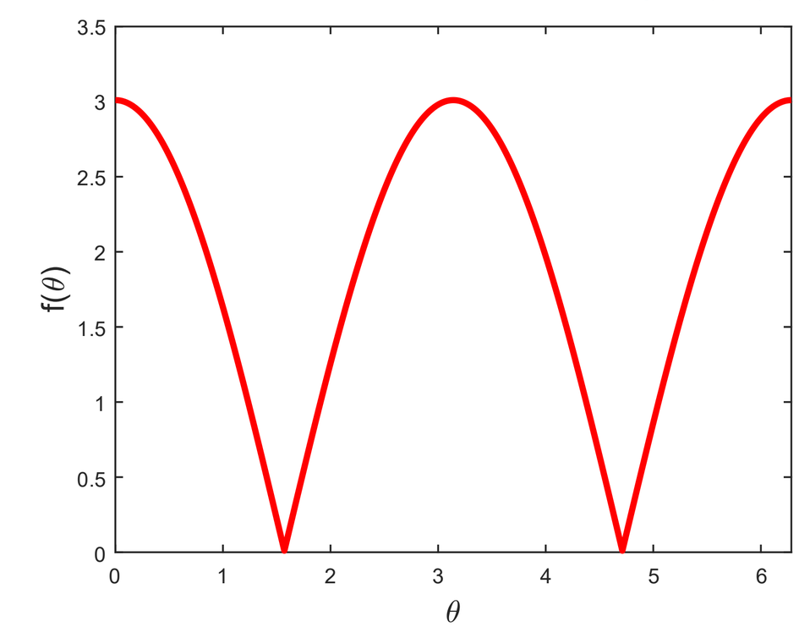
Functional form of $f(\theta)$



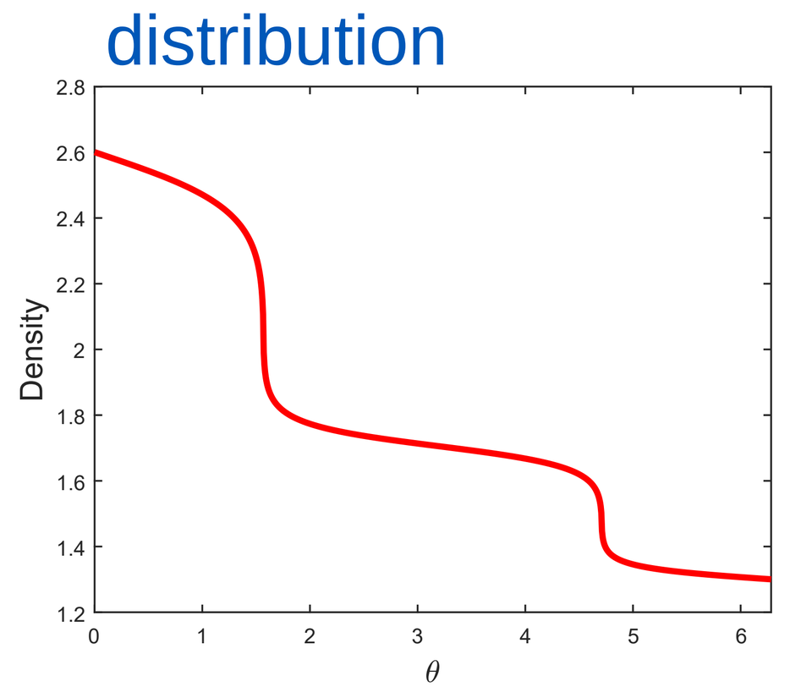
Steady state phase distribution



Functional form of $f(\theta)$



Steady state phase distribution



DISCUSSION

- Tricycle assigns cell cycle phase along a continuum form 0 to 2π and can be applied to any sc/snRNAseq dataset to accurately infer cell cycle position. We apply it to a newly published snRNAseq dataset for GBM[1].
- The gl_Pro GBM subtype has by far the greatest number of actively dividing cells, while gl_PN and gl_Mes have relatively few cells actively cycling cells. This is shown by the high density of gl_Pro cells found between $0.5\pi - 1.5\pi$.
- We develop a simple phase structured mathematical model for cell cycle progression. We show that it can produce many different steady state phase distributions, some of which recapitulate phase distributions observed from biological data.

FUTURE WORK

- Calibrate our mathematical model to the three GBM subtypes.
- Further investigate how different functional forms of $c(t,\theta,g), d(t,\theta)$ and $K(t,\theta)$ affect the steady state phase distribution.

REFERENCES

1. Al-Dalahmah et al., Nature Communications, 2023
2. Zheng et al., Genome Biology, 2022
3. Schwabe et al., Molecular systems Biology, 2020

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