

Towards a digital twin of BCP-ALL: logical models of B-Cell differentiation identify gene dependencies

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INTRODUCTION

B-cell Precursor Acute Lymphoblastic Leukaemia (BCP-ALL) is a well-characterized paediatric cancer driven by complex genetic alterations that induce a B-cell differentiation arrest (1). While the end-states of this malignancy have been extensively detailed through high-throughput sequencing techniques, the temporal dynamics of carcinogenesis remain largely unobservable. Consequently, the acquisition of new data for interception strategies is essential; *in silico* modelling, leveraged by clinical data describing these terminal states, provides a vital opportunity to reconstruct and understand disease development, a prerequisite for more personalized medicine.

METHODS

The B-cell differentiation process was captured using a multivalued logical model implemented in **BioModel Analyzer (BMA)(2)**. Each regulatory element is represented as a node with a discrete integer state variable:

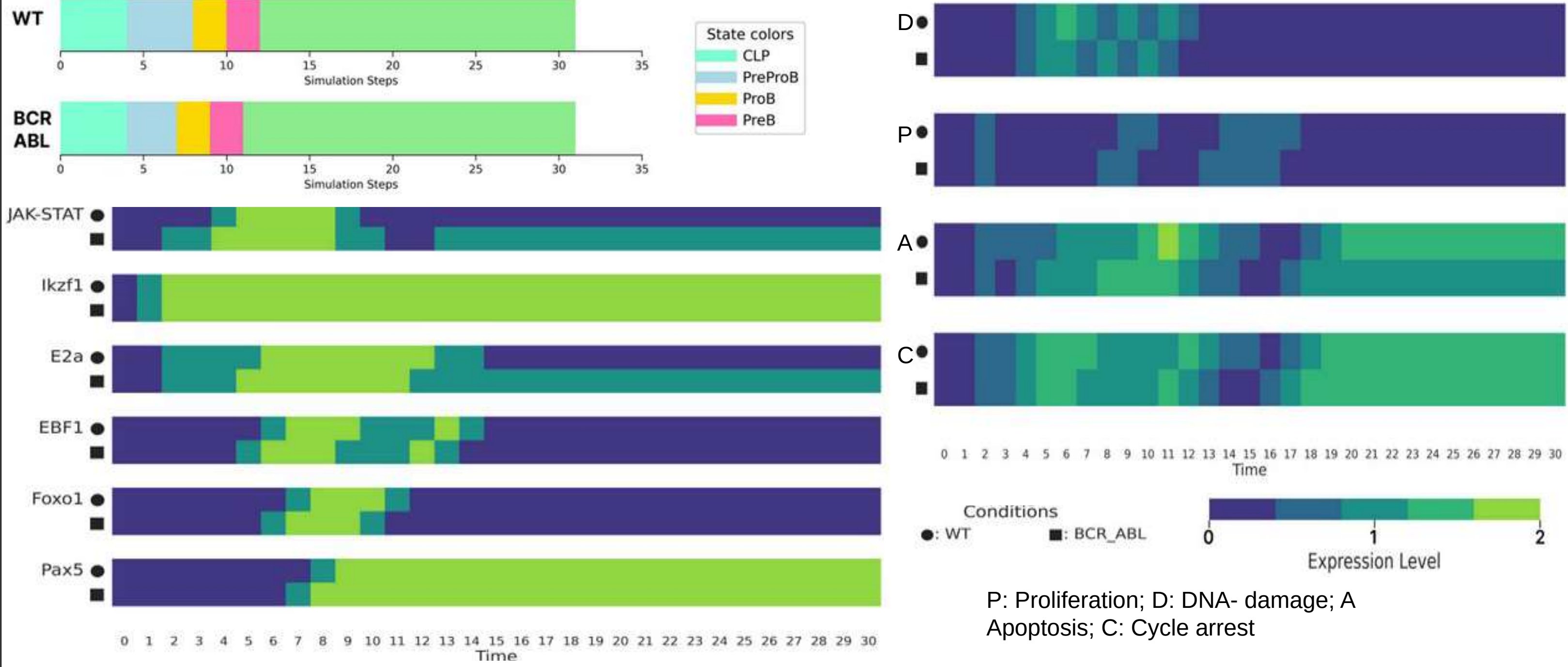
Genetic Nodes (k=3): To incorporate patient-specific clinical data, genetic loci are modeled with three functional states:

0: Inactive or homozygous deletion; 1: Heterozygous deletion; 2: Wild-type (normal) status.

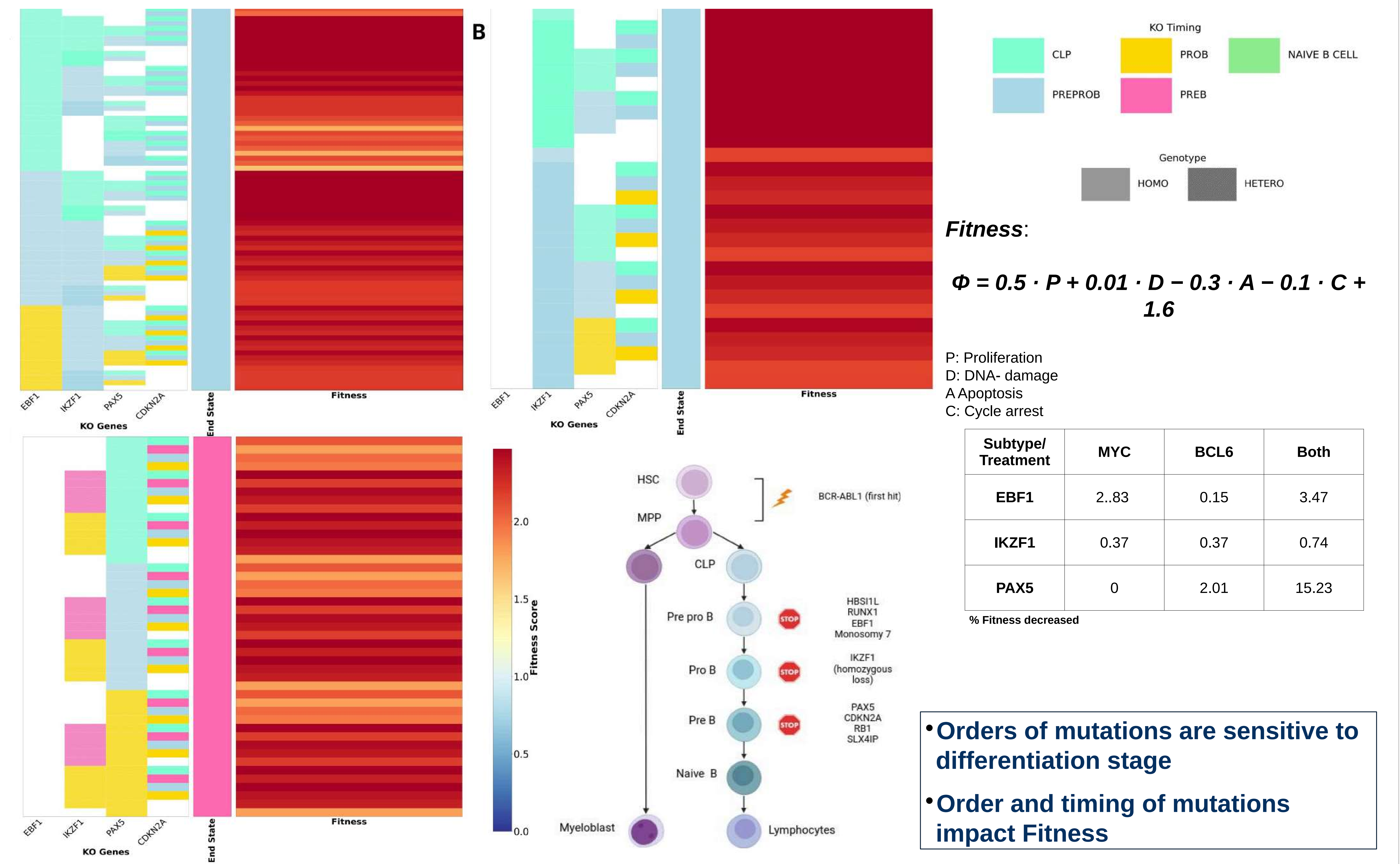
Phenotypic Nodes (k=5): Markers representing biological processes, such as Apoptosis and Proliferation,

We simulated various BCR-ABL mutation profiles derived from clinical datasets (3-4). These simulations were employed to: i) Identify the potential temporal order of mutational events, ii) Predict how specific genetic deletions perturb the stability of the B-cell network.

RESULTS



BCR-ABL accelerates differentiation but is insufficient in isolation to induce leukaemogenesis



Conclusion

We present a personalized multivalued logical model of B-cell differentiation, allowing to study the carcinogenesis of different BCR-ABL profiles derived from clinical data. Using the model we demonstrate how the order and timing of genetic alteration influence the development of the BCR-ABL subtype and how these factors impact treatment response following the application of combined MYC/BCL6 therapy.

1) Mullighan, C.G., et al.: Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature 446(7137), 758–764 (2007)
2) Benque, D. et al. Bma: Visual tool for modeling and analyzing biological networks. In: International Conference on Computer Aided Verification, pp. 686–692 (2012). Springer
3) Kim, J.C., et al.: Transcriptomic classes of bcr-abl1 lymphoblastic leukemia. Nature genetics 55(7), 1186–1197 (2023)
4) Iacobucci, I., et al.: Multipotent lineage potential in b cell acute lymphoblastic leukemia is associated with distinct cellular origins and clinical features. Nature Cancer, 1–26 (2025)