

A predictive computational model of hematopoietic stem cell differentiation kinetics in culture

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Hematopoietic stem cells (HSCs) maintain the body's full complement of blood and immune cells *in vivo* via complex signaling cascades between multiple components in the bone marrow niche. Imitating these interactions *in vitro* for obtaining clinically relevant HSC populations remains a challenge. A computational approach has the potential to systematize these interactions to enable a better understanding of their kinetics. Here we describe a model investigating the kinetics driving early lineage specification of HSCs in culture. The balance between HSC self-renewal and differentiation, determined by cell-secreted paracrine signaling molecules in culture is examined.

Primary HSCs isolated from murine bone marrow were cultured *in vitro* over 9 days. Their proliferation and differentiation state was determined via flow cytometry to identify primitive progenitors: long-term (LT-HSC), short-term (ST-HSC), multipotent progenitors (MPP) and common myeloid progenitors (CMP) (Fig. 1). We utilized the STELLA modeling and simulation software along with Berkeley Madonna to develop a dynamic model of the culture system. Experimental data gathered over multiple days was used to validate and refine the model.

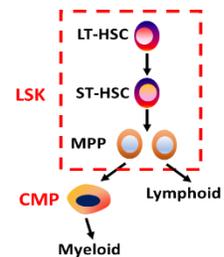


Fig.1 HSC hierarchy

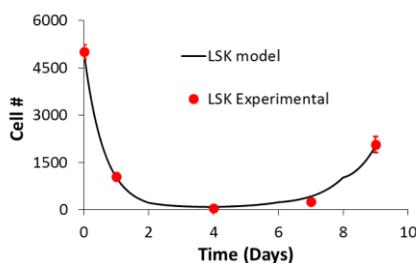


Fig.2 Comparing experimental and model data

Experimentally, the initial decline in LSK numbers is contrasted by a dynamic rise and fall of the CMP population; whereas the differentiated cells show exponential growth over time. These varied profiles indicate an active, feedback-mediated trade-off between differentiation vs. proliferation rates for all cell types. The computational model was successfully able to replicate the biological data for the LSK (Fig. 2), CMP and differentiated cell populations. A closer look at the LSK sub-fractions indicated relatively constant LT-HSC and MPP numbers but a proliferative ST-HSC growth, suggesting they are primarily responsible in generating downstream cell populations.

This model enables investigation of the balance between HSC proliferation and differentiation, as a function of dynamic, cell-regulated feedback within the system. It also provides an opportunity to optimize their growth kinetics and develop platforms for directed cell expansion.

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