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# Feedback mechanisms control coexistence in a stem cell model of acute myeloid leukaemia

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## HIGHLIGHTS

- Models of competition between cell populations can describe the progression of acute myeloid leukaemia.
- We identify regions of coexistence in which leukaemia and healthy haematopoietic species can coexist in the niche.
- The dynamics of progenitor cells exert key control over species coexistence.
- The introduction of regulatory feedback can promote healthy haematopoiesis and suppress leukaemia.

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## ABSTRACT

Haematopoietic stem cell dynamics regulate healthy blood cell production and are disrupted during leukaemia. Competition models of cellular species help to elucidate stem cell dynamics in the bone marrow microenvironment (or niche), and to determine how these dynamics impact leukaemia progression. Here we develop two models that target acute myeloid leukaemia with particular focus on the mechanisms that control proliferation via feedback signalling. It is within regions of parameter space permissive of coexistence that the effects of competition are most subtle and the clinical outcome least certain. Steady state and linear stability analyses identify parameter regions that allow for coexistence to occur, and allow us to characterise behaviour near critical points. Where analytical expressions are no longer informative, we proceed statistically and sample parameter space over a coexistence region. We find that the rates of proliferation and differentiation of healthy progenitors exert key control over coexistence. We also show that inclusion of a regulatory feedback onto progenitor cells promotes healthy haematopoiesis at the expense of leukaemia, and that – somewhat paradoxically – within the coexistence region feedback increases the sensitivity of the system to dominance by one lineage over another.



## 1. Introduction

Acute myeloid leukaemia (AML) is a cancer of the blood that causes expanded clones in the myeloid lineage, disrupting healthy haematopoiesis (Löwenberg et al., 1999). Healthy haematopoiesis is governed by a population of haematopoietic stem cells (HSCs), which reside in a stem cell niche within the bone marrow (Wang and Wagers, 2011), and are responsible for the production of all red blood cells, white blood cells, and platelets (Orkin and Zon, 2008). HSCs constitute a rare population of haematopoietic cells, and, through successive symmetrical or asymmetric divisions, they can lose their capacity for unlimited self-renewal and become lineage-restricted committed progenitor cells, before they eventually become terminally differentiated and specialised. This hierarchical organisation helps to protect against malignant transformation within haematopoietic cell lineages.

The cancer stem cell theory proposes that only a subpopulation of cancer cells are responsible for cancer growth and have the capacity to metastasise; they may also be resistant to treatment. This population is referred to as cancer stem cells, and shares characteristics with its healthy counterpart stem cell population in various tissues (Dean et al., 2005). The cancer stem cell theory has, however, been contentious at times, as functional and molecular characterisation of cancer stem cells remains elusive (Woll et al., 2014; Clevers, 2011).

Only a subpopulation of leukaemia cells have the ability to reconstitute the disease following transplantation; we assume in this work that these are cancer stem cells and refer to them as leukaemia stem cells (LSCs). Their existence was first demonstrated by Lapidot et al. (1994) in AML. Later studies found further

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evidence for the hierarchical organisation of AML (Bonnet and Dick, 1997; Cozzio et al., 2003). Important questions regarding LSCs include whether they are indeed rare (Lane et al., 2009; Quintana et al., 2008), and whether they most closely resemble HSCs or a haematopoietic progenitor cell population (Passegué et al., 2003; Goardon et al., 2011; Lane et al., 2011; Cabezas Wallscheid et al., 2013). It has been shown mathematically that LSCs could comprise any fraction of a blood cancer (Johnston et al., 2010).

A further question, which we believe is fundamental to understanding cancer progression, regards how cancer interacts and competes with the healthy populations in its surroundings. Here, limited experimental research exists (Schuurhuis et al., 2013), and mathematical modelling helps us to address mechanisms of disease and make predictions. Several models have been developed to study leukaemia in general (Roeder and Loeffler, 2002; Michor et al., 2005; Roeder et al., 2006; Horn et al., 2013; Foo et al., 2009; Tang et al., 2011; MacLean et al., 2014; Colijn and Mackey, 2005; Moore and Li, 2004; Werner et al., 2013), and AML in particular (Andersen and Mackey, 2001; Liso et al., 2008; Cucuianu and Precup, 2010; Stiehl and Marciniak-Czochra, 2012; Stiehl et al., 2014). Stiehl et al. (2014) present an attractive model of acute leukaemias, and demonstrate the importance of parameters controlling self-renewal in both diagnosis and relapse. Here, we use a similar modelling framework however our goals and subsequent methods of analysis are different. We seek to characterise how competition processes between healthy and leukaemia stem cells affect species coexistence and disease outcome. The cancer stem cell hypothesis forms a key assumption of our work here, as does the hypothesis that an ecological niche description is required to understand cell interactions within the bone marrow microenvironment.

Certain studies have suggested that the LSC population within AML often shares more features with a progenitor cell population than a stem cell population (Passegué et al., 2003; Goardon et al., 2011), although it is also possible that both stem-like and progenitor-like leukaemia populations coexist (Cabezas Wallscheid et al., 2013). Until recently, little was known about the population dynamics of specific haematopoietic lineages during the progression of AML: this is changing. Cabezas Wallscheid et al. (2013) show that, following expression of the oncogenic fusion protein AML1-ETO, haematopoietic cell lineages are disrupted in particular ways during the path towards leukaemia. A loss of lymphocytes and erythrocytes is accompanied by a dramatic rise in the size of myeloid populations. In the more primitive haematopoietic compartments, changes to population size were not seen: the leukaemic transformation events take place in primitive stem and progenitor cell compartments, affecting the myeloid and lymphoid progeny.

We seek to understand in greater depth the shape of competition during disease progression by modelling the interactions and feedbacks between leukaemia and haematopoietic species, specifically, we model competition occurring between LSCs and healthy progenitor cells. In addition to the role that progenitors play in leukaemia, there is growing evidence that this population plays a greater role in haematopoiesis than had previously been assumed, promoting the idea that a renewed focus on the dynamics of haematopoietic progenitor cells is warranted (Sun et al., 2014). Recent work has shown how AML disrupts haematopoiesis by forming malignant niches capable of sustaining disease, highlighting leukaemia's ability to dramatically affect haematopoietic niches (Hanoun et al., 2014). Based on previous work that provided insight into competition within the HSC niche (MacLean et al., 2013), here we develop two new models that differ in their treatment of signalling between progenitor and terminally differentiated haematopoietic cells.

In the next section we introduce the models and describe their basic properties. We go on to analyse model behaviour using a combination of analytical and numerical techniques, to identify what factors control the competition between LSCs and progenitor cells. We are particularly interested in those regions of behaviour space that allow for coexistence between leukaemia and haematopoietic species, as these are most crucial in determining clinical outcome.

## 2. Competition models of acute myeloid leukaemia

Two new models are proposed that each describes the dynamics of AML in the bone marrow. They differ subtly, regarding mechanisms of feedback that we wish to compare. Each contains five cellular species, the dynamics of which are described by ordinary differential equations (ODEs).

Competition models are based upon the ideas introduced by Lotka and Volterra and later ecologists (Lotka, 1920; Volterra, 1926; May and MacArthur, 1972). Ecological concepts can also be applied in a cellular context, such as within the stem cell niche (MacLean et al., 2013; Mangel and Bonsall, 2013). Here, competing species share a reliance on finite environmental resources including nutrients, cofactors, and molecular signals which are essential for their functionality. Even though we expect feedback effects to increase faster as competing species accumulate — i.e. crowdedness within the niche amplifies regulatory signals, — we assume them to be (i) *linear* and (ii) *proportional* to the population sizes of all species involved.

The diverse types of blood cells encountered in the body are derived from a self-renewing population of haematopoietic stem cells (HSCs – or species $S$ in the model), which can differentiate into multipotent progenitor cells, and eventually terminally differentiated cells. Given that we focus on the dynamics of differentiation and blood cell production, we group the various haematopoietic species into two populations: haematopoietic progenitor cells ($A$), and specialised, terminally differentiated blood cells ($D$), similar to previous work (MacLean et al., 2013).

In the following models AML consists of two distinct cell populations: a proliferating leukaemia cell population ($L$); and a population of terminally differentiated leukaemia cells ($T$). Proliferating leukaemia cells are assumed to be in competition with haematopoietic progenitor cells, rather than HSCs. Thus HSC dynamics are not directly impacted by AML, although there will be an indirect effect through feedback. Although we refer to population $L$ as leukaemia stem cells (LSCs), this does not refer to their cell of origin, but only to their lineage-maintaining characteristics (Dick, 2008). Additionally, in this work we consider questions about cancer progression, and leave the matter of cancer incidence for elsewhere.

### 2.1. Model I

We describe the dynamics of the five species introduced above with a system of ODEs. A schematic description of the Model I is given in Fig. 1; and the model is specified by the following equations:

$$\frac{dS}{dt} = \rho_S S(K_1 - Z_1) - \delta_S S \tag{1a}$$

$$\frac{dA}{dt} = \delta_S S + \rho_A A(K_2 - Z_2) - \delta_A A \tag{1b}$$