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# Dynamic self-organisation of haematopoiesis and (a)symmetric cell division

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ABSTRACT

A model of haematopoiesis that links self-organisation with symmetric and asymmetric cell division is presented in this paper. It is assumed that all cell divisions are completely random events, and that the daughter cells resulting from symmetric and asymmetric stem cell divisions are, in general, phenotypically identical, and still, the haematopoietic system has the flexibility to self-renew, produce mature cells by differentiation, and regenerate undifferentiated and differentiated cells when necessary, due to self-organisation. As far as we know, no previous model implements symmetric and asymmetric division as the result of self-organisation. The model presented in this paper is inspired by experiments on the *Drosophila* germline stem cell, which imply that under normal conditions, the stem cells typically divide asymmetrically, whereas during regeneration, the rate of symmetric division increases. Moreover, the model can reproduce several of the results from experiments on female Safari cats. In particular, the model can explain why significant fluctuation in the phenotypes of haematopoietic cells was observed in some cats, when the haematopoietic system had reached normal population level after regeneration. To our knowledge, no previous model of haematopoiesis in Safari cats has captured this phenomenon.

## 1. Introduction

*Haematopoiesis* is the generation of the blood-forming system. At the root of this process is a small group of slowly replicating cells, the *haematopoietic stem cells*, which are undifferentiated cells with the capacity to both *self-renew* and generate all types of blood cells (Baum et al., 1992; Morrison and Weissman, 1994). The haematopoietic stem cells are located within the bone marrow and segregated among different bones throughout the body. Through sequential division, the haematopoietic stem cells differentiate into *progenitor cells*, which in turn differentiate into red blood cells, white blood cells or platelets. Since the number of haematopoietic stem cells is much smaller than the number of more differentiated blood cells, the haematopoietic stem cells must be protected and tightly regulated. *Haematopoietic bone marrow niches*, which are restricted regions in the bone marrow that contain undifferentiated cells and support stem cell behaviour, may be crucial in both aspects (Wineman et al., 1996; Lemischka, 1997; Bertolini et al., 1997; Aiuti et al., 1998; Thiemann et al., 1998; Verfaillie, 1998; Koller et al., 1999; Yin and Li, 2006; Zhang and Li, 2008; Cheng et al., 2014). Since it is not possible to reconstruct a niche experimentally, it is difficult to maintain haematopoietic stem cells in vitro, because signals from the niche affect stem cell survival, self-renewal, and differentiation. This is one of the reasons why relatively little is known about the exact behaviour of haematopoietic stem cells. On the other hand, haematopoietic progenitors have been studied both in vivo and in vitro (Abkowitz et al., 1988, 1990, 1993; Gehling et al., 2000; Akita et al., 2013; Herrmann et al., 2014). A set of experiments was designed by Abkowitz et al., using female *Safari cats*, in order to get an idea of the contribution of haematopoietic stem cells to progenitor cells (Abkowitz et al., 1988, 1990, 1993). The Safari cat is a hybrid of the Geoffroy cat (a South American wildcat) and a domestic cat (which is of Eurasian origin). These two species have evolved independently for twelve million years, and have distinct phenotypes of the X chromosome-linked enzyme glucose-6-phosphate dehydrogenase (G6PD) (Molecular genetics in the domestic cat and its relatives, 1986). Female Safari cats have some cells that contain Geoffroy-type G6PD (G G6PD) and other cells that contain domestic-type G6PD (d G6PD). The G6PD phenotype is retained after replication and differentiation, and is functionally neutral. Therefore, it provides a binary marker of each cell and its offspring. In particular, this means that a progenitor cell that expresses G G6PD is the daughter of a stem cell that expresses G G6PD, and likewise, a progenitor cell that is d G6PD-positive is the daughter of a stem cell that is d G6PD-positive. Abkowitz et al. (1988), Abkowitz et al. (1990), Abkowitz et al. (1993) tracked the contributions of haematopoietic stem cells to the progenitor cells by observing the G6PD phenotype of haematopoietic progenitor cells. In the first trials,

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the percentage of committed progenitor cells expressing d G6PD was observed over a period of almost six years in normal female Safari cats, and Abkowitz et al. found that the percentage remained relatively constant (Abkowitz et al., 1988, 1990). On the contrary, the G6PD phenotype of haematopoietic progenitors varied extensively when six Safari cats were lethally irradiated, in order to kill the cells in their bone marrow, and a small number of bone marrow cells, collected prior to the radiation, were transplanted back (Abkowitz et al., 1990, 1993). Abkowitz et al. observed the percentage of progenitor cells expressing d G6PD while the cells in the bone marrow regenerated, and they found that the pattern of clonal contribution to haematopoiesis in each cat was unique. For instance, some of the cats that both had cells expressing d G6PD and cells expressing D G6PD when the regeneration started, had only cells expressing either d G6PD or D G6PD when the production of bone marrow cells stabilised after regeneration. Thus, one of the phenotypes had got extinct during the regeneration. On the contrary, in other cats, the percentage of cells expressing d G6PD and D G6PD remained on average relatively constant. Moreover, in some cats, significant variation in the percentage extended for years after the number of cells reached normal population levels, whereas in other cats, the percentage remained approximately constant. Several mathematical models (Guttorp et al., 1990; Newton et al., 1995; Abkowitz et al., 1996; Golinelli et al., 2006; Fong et al., 2009) have been proposed to explain the results from the experiments on female Safari cats (Abkowitz et al., 1988, 1990, 1993). These models are discussed in Section 1.4.

### 1.1. Symmetric and asymmetric stem cell division

Stem cells are, in general, undifferentiated cells that can both self-renew and generate differentiated progeny required by a given tissue (Morrison et al., 1997; Reya et al., 2001). An important aspect is the fate of the two daughter cells when a stem cell divides (Yamashita et al., 2003; Morrison and Kimble, 2006; McKenzie et al., 2006; Dingli et al., 2007). If one daughter cell has stem cell identity and the other daughter cell commits to differentiation and loses the stem cell identity, it is called as an *asymmetric stem cell division* or *asymmetric self-renewal*. Under normal conditions, the number of cells in a given tissue is approximately constant. It is generally believed that the number of stem cells is also approximately constant under normal conditions, and that they differentiate and self-renew at relatively constant rates to replace mature cells and to keep the stem cell number at a certain normal level (Wichmann et al., 1988; Shortman and Naik, 2007). By dividing asymmetrically, the stem cells manage to both self-renew and produce differentiated cells in a single division. The experiments by Abkowitz et al. indicate that haematopoietic cells divide asymmetrically under normal conditions, because the percentage of cells expressing d G6PD remained relatively constant when normal female Safari cats were observed over a period of almost six years (Abkowitz et al., 1988, 1990). However, a disadvantage of asymmetric stem cell division is that it leaves stem cells unable to expand in number. It is, in general, believed that the stem cells can regenerate (Morrison et al., 1997; Reya et al., 2001; Yamashita et al., 2003; Morrison and Kimble, 2006; McKenzie et al., 2006; Dingli et al., 2007). In particular, haematopoietic stem cells can expand rapidly in response to injury to the bone marrow, such as stem cell transplantation (Abkowitz et al., 1990, 1993; McKenzie et al., 2006). Hence, asymmetric self-renewal cannot be the complete story, since it leaves stem cells unable to expand in number.

*Symmetric division* is defined as generation of daughter cells destined to acquire the same fate. In this paper, symmetric stem cell division is defined as *symmetric self-renewal* if both daughter cells are stem cells and *symmetric commitment* if none of the daughters are stem cells. The number of stem cells increases by one after symmetric self-renewal. Hence, since the haematopoietic bone marrow can regenerate after injury (Abkowitz et al., 1990, 1993; McKenzie et al., 2006), it is likely that the rate of symmetric self-renewal depends on the number of haematopoietic stem cells. On the contrary, the number of stem cells decreases by one after a symmetric commitment. Thus, this type of division can cause the extinction of a stem cell phenotype. The experiments on female Safari cats indicate that both types of symmetric stem cell division occur when the haematopoietic bone marrow niche regenerates after injury (Abkowitz et al., 1990, 1993). Wide fluctuation in the percentage of progenitors with d G6PD was observed for one to four years, before the percentage stabilised and became relatively constant. This indicates that when there are significantly less haematopoietic stem cells in the niche than under normal conditions, the rate of symmetric self-renewal increases such that the number of haematopoietic stem cells also increases. When the number of haematopoietic stem cells reaches its normal population level, the rate of symmetric self-renewal decreases, and proliferation in the haematopoietic niche stabilises. Moreover, some of the cats that both had cells expressing d G6PD and D G6PD when the regeneration started, only had cells expressing either d G6PD or D G6PD when the production of bone marrow cell stabilised after regeneration. This indicates that the haematopoietic stem cells commit symmetrically to differentiation under regeneration, since this type of division can cause the extinction of a phenotype. Clearly, the rate of symmetric self-renewal must, on average, be higher than the rate of symmetric commitment when the haematopoietic niche regenerates, such that the number of stem cells increases. On the other hand, under normal conditions, the number of stem cells remains constant, and hence, the two types of symmetric division must occur at the same rate. Thus, the experiments by Abkowitz et al. indicate that haematopoietic stem cells divide mostly asymmetrically under normal conditions, whereas when the haematopoietic bone marrow niche regenerates after injury, the haematopoietic stem cells start to divide symmetrically (Abkowitz et al., 1988, 1990, 1993; McKenzie et al., 2006). Does this mean that a stem cell “knows” that it must divide asymmetrically under normal conditions and self-renew symmetrically when stem cells need to be replaced? This would also imply that the daughter cells inherit this “knowledge”. As discussed by Loeffler and Roeder (2002), the assumption that each cell “knows” how to behave in different situations is too rigorous and potentially misleading. In the next subsection, it is argued that each stem cell behaves completely random. However, the stem cells divide mostly asymmetrically under normal conditions and symmetrically under regeneration due to dynamic regulation and self-organisation in the haematopoietic bone marrow niche.

Several mathematical models that include symmetric and asymmetric stem cell division have been proposed (Abkowitz et al., 1988, 1990, 1993; Dingli et al., 2007; Wodarz and Komarova, 2005). Wodarz and Komarova (2005) present a model where the haematopoietic stem cells only divide asymmetrically under normal conditions, whereas during regeneration, the stem cells switch to symmetric division. On the contrary, in the model proposed by Abkowitz et al. (1996), the haematopoietic stem cells can only divide symmetrically: Under normal condition, the stem cells undergo symmetric self-renewal and symmetric commitment at the same, constant rate, and under regeneration, the rate of the former type of division increases. Even though all the models presented in Abkowitz et al. (1988), Abkowitz et al. (1990), Abkowitz et al. (1993), Dingli et al. (2007), Wodarz and Komarova (2005) capture important aspects related to stem cell behaviour, it is a drawback that stem cell self-renewal and differentiation do not depend on local growth conditions. The model proposed by Roeder and Loffler in Loeffler and Roeder (2002) and Roeder and Loeffler (2002) considers the dependence of proliferation control on the local growth conditions. However, no implications about symmetric or asymmetric stem cell division are included in this model.

### 1.2. Haematopoietic bone marrow niche

The haematopoietic bone marrow niche is composed of both localised signalling cells and an extracellular matrix that control the