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Lorenz system in the thermodynamic modelling of leukaemia malignancy

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ABSTRACT

The core idea of the proposed thermodynamic modelling of malignancy in leukaemia is entropy arising within normal haematopoiesis. Mathematically its description is supposed to be similar to the Lorenz system of ordinary differential equations for simplified processes of heat flow in fluids. The hypothetical model provides a description of remission and relapse in leukaemia as two hierarchical and qualitatively different states of normal haematopoiesis with their own phase spaces. Phase space transition is possible through pitchfork bifurcation, which is considered the common symmetrical scenario for relapse, induced remission and the spontaneous remission of leukaemia. Cytopenia is regarded as an adaptive reaction of haematopoiesis to an increase in entropy caused by leukaemia clones. The following predictions are formulated: a) the percentage of leukaemia cells in marrow as a criterion of remission or relapse is not necessarily constant but is a variable value; b) the probability of remission depends upon normal haematopoiesis reaching bifurcation; c) the duration of remission depends upon the eradication of leukaemia cells through induction or consolidation therapies; d) excessively high doses of chemotherapy in consolidation may induce relapse.

Introduction

Traditionally, leukaemia is considered to be a unidirectional process of the growth and expansion of leukaemia clones into bone marrow. The resulting failure of normal haematopoiesis and the involvement of other organs are regarded as complications of the disease. The corresponding model of leukaemia as a proliferating tumour is based on its numerical aspect – the number of leukaemia cells over time. Another aspect of leukaemia – the malignant effect of leukaemia cells on normal haematopoiesis – is often overlooked in modelling, despite the fact that it greatly determines the course of the disease and the survival prognosis for the patient.

This article presents a model of leukaemia malignancy as a process of entropy arising within normal haematopoiesis, caused by leukaemia clones. Why are thermodynamics needed in the description of leukaemia and what can be expected from it? Thermodynamics explains why something happens but does not show how it happens. It does not provide a description of molecular mechanisms behind relapse or the remission of leukaemia; however it explains why spontaneous processes in leukaemia are possible. Thermodynamics provides a more accurate description of the nonlinear aspect of leukaemia dynamics than computational models of proliferating leukaemia clones.

A mathematical description of entropy arising within normal haematopoiesis in leukaemia is somewhat similar to entropy arising in heating a shallow layer of fluid, known as the Lorenz system. The role of leukaemia clones in this context appears to be only that of a passive "heat" source, while induced remission, spontaneous remission and relapse are considered common manifestations of the same process of phase space transition through bifurcation in normal haematopoiesis.

The greatest weakness of this model is the presentation of remission and relapse as two *qualitatively* different states of haematopoiesis in leukaemia. The lack of experimental evidence for molecular mechanisms specific to remission or relapse can leave this model unsubstantiated. In addition, the model cannot easily be applied to the analysis of solid cancers as the modelling conditions are different.

Thermodynamics provides a powerful tool for modelling different aspects of leukaemia and thus it seems possible to build several thermodynamic models as alternatives to the traditional linear model of leukaemic clone expansion. The non-equilibrium aspect of leukaemia might be modelled as a two-component unbalanced system of normal haematopoiesis and leukaemic cloning generating a biological oscillator with entropy flow between its parts. A

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hybrid model of leukaemia as a process of entropy arising within normal haematopoiesis and an upper level model of leukaemia as a biological oscillator might be a next step in our modelling efforts.

Leukaemia: problem review

Leukaemia as a disease

Leukaemia is a group of cancers involving the blood cells of the bone marrow. Leukaemia is the 11th most common cancer worldwide, with around 352,000 new cases diagnosed in 2012 [1]. Malignant transformation usually occurs at the level of a pluripotent stem cell or committed progenitor cells with more limited capacity for differentiation. It is generally accepted that an abnormally high proliferation rate and longevity lead to the expansion of leukaemic clones in bone marrow and often into various other organs and sites, such as the liver, spleen, lymph nodes, central nervous system, kidneys and gonads. The resulting disruption of haematopoiesis causes anaemia, infection, easy bruising or bleeding. In a typical case of acute leukaemia, such symptoms are usually present for only days to weeks before diagnosis. It has been estimated that approximately 10^{12} leukaemia cells will be present by that time [2], which indicates that the growing leukaemic clones coexist with normal haematopoiesis for months without any apparent signs of its presence.

New mutations in leukaemic clones as a basis for leukaemia progression

Relatively recent experimental evidence suggests that acute myeloid leukaemia may originate from multiple clones of malignant cells [3]. For chronic lymphocytic leukaemia, certain genetic events, considered to be "clonal driver mutations", are found in the majority of cells, whereas others, present only in a fraction of the tumour, are deemed to be "subclonal driver mutations" [4]. Sequencing studies have revealed about 140 genes that when altered by intragenic mutations can act as driver mutations during tumorigenesis [5]. The presence of sub-clonal driver mutations has been associated with reduced survival in chronic lymphocytic leukaemia [6] and it seems that the degree of subclonality might serve as a cancer marker *per se*. Higher diversity is related to a higher mutation rate or longer tumour evolution with more replications [7].

Possible mechanisms of normal haematopoiesis disruption in leukaemia

The interaction between healthy and cancer cell lines is often described as a competition for physical space resulting in increased cellular degradation. This is consistent with the observation of an increase of markers for cell death, such as lactate dehydrogenase [8–11]. Several mechanisms underlying this spatial competition have been proposed: overcrowding, which results in the extinction of cells [12]; competition for a limited surface niche expressing certain receptors [13,14]; apoptosis if no contacts to these receptors can be established [15]. Other possible mechanisms include the induction of cytopoenia by impeding the proliferation and differentiation of haematopoietic stem cells [16] and competition for energy and nutrients [17]. Although the molecular mechanisms of disruption are not known, at the level of cell populations, haematopoiesis disruption is consistent with the competitive exclusion principle (also known under several other names, including Lotka–Volterra Law), which postulates that populations competing for the same limited resource in one homogeneous habitat cannot coexist for long [18,19]. However, it is still debatable whether the competitive exclusion principle developed for ecosystems can be applied to processes at the cellular level.

Clinical remission and relapse as two states of haematopoiesis in leukaemia

The first manifestation of leukaemia concerns not only the expansion of leukaemia clones into the marrow and other organs, but also the disruption of normal haematopoiesis, leading to severe complications of the disease. The goal of induction therapy for leukaemia is to attain complete remission, which usually requires a period of marrow aplasia, or a "morphologic leukaemia-free state", following induction chemotherapy [2]. Complete remission is currently defined as the restoration of normal haematopoiesis with a blast cell fraction of less than 5% determined by light microscopic examination of the bone marrow. This relatively liberal definition reflects the difficulty of identifying leukaemic blasts in regenerating marrow by morphologic criteria alone. Thus, patients with nearly 5% leukaemic blast cells in their marrow specimens can harbour as many as 10^{10} leukaemia cells [20,21]. The recurrence of leukaemia after therapy, called relapse, is a common problem. The goal of post-remission or consolidation therapy is to prolong complete remission by delaying or preventing relapse and maximizing the chance of a cure [2]. In typical acute leukaemia with chemotherapy the leukaemic process is staged strictly as relapse or remission, while correlations between the kinetic parameters of the normal and leukaemic populations are suggested to characterize the leukaemic state [22].

Spontaneous remission of leukaemia

The remission of leukaemia without any specific therapy, called spontaneous remission, is an extremely rare and exceptional phenomenon, relatively well documented but poorly understood. Spontaneous remission of acute myeloid leukaemia is almost always a transient event, with a mean duration in the literature of 7.7 months (range 1–36) [23]. In a typical case of spontaneous remission, the full restoration of normal haematopoiesis and the disappearance of blast cells occur in patients with acute leukaemia and concurrent infection [23–34], blood transfusion [23–25,31,35] or cytokine injection [36,37]. The underlying molecular mechanisms of spontaneous remission are still unknown. The activation of cytotoxic T lymphocytes and macrophages, in conjunction with an increased cytotoxicity of natural killer cells [38] as well as cytokines of the immune system, such as tumour necrosis factor [39,40], interferon gamma and interleukin-2, released during infection, may play a role in the occurrence of spontaneous remission [41,42]. However, no clear link between spontaneous remission and infection or immune response was reported in at least one case [43]. In another report, spontaneous remission was detected after the termination of pregnancy [44].

The Lorenz system and the main hypothesis

Dynamic biological or physical systems display a variety of linear and nonlinear behaviours that can be described using corresponding mathematical models. Despite the diverse nature of such processes, the resulting mathematical description is often quite similar, so it seems possible to gain insight into the onset and progression of leukaemia by considering some aspects of the dynamics of the disease with the help of other models. This idea of common mathematical description is widely used for modelling in biology and will be used here to highlight similarities between leukaemia and heat distribution in fluid flows.