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LORENZ SYSTEM IN THERMODYNAMICAL MODELLING OF LEUKEMIA

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"My proofs were always wrong,
and yet it was all obvious anyway.
You could see just by the diagrams."
A.Porges. Devil and Simon Flagg.

Graphical solutions of ordinary differential equations for simplified processes of heat flow in fluids (Lorenz system) and an idea of common mathematical description are the basis for the presented thermodynamical leukemia model. The model provides description of normal hematopoiesis in leukemia as two hierarchical steady states corresponding to remission and relapse. Transition between them is possible through pitchfork bifurcation which is considered as the common symmetrical mechanism for the phase space changes in leukemia. The phenomenon of spontaneous remission is explained. Cytopenia is considered as an adaptive reaction of hematopoiesis to entropy increase caused by leukemic clone. The following hypotheses are formulated: a) percentage of leukemia cell in marrow for relapse or remission criterion is not strict cut-off constant but a variable value; b) Probability of getting remission depends upon reaching bifurcation; c) Length of remission depends upon degree of eradication of leukemia cells in induction.

1 Introduction.

1.1 Leukemia as a disease. Leukemia is a group of cancers involving blood cells of bone marrow. Leukemia is the 11th most common cancer worldwide, with around 352,000 new cases diagnosed in 2012 *[16]*. 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 abnormally high proliferation rate and longevity lead to expansion of leukemic clone in bone marrow and often into various other organs and sites, such as liver, spleen, lymph nodes, central nervous system, kidneys and gonads. Resulting disruption of hematopoiesis cause anemia, infection, easy bruising or bleeding. In a typical case of acute leukemia such symptoms have usually been present for only days to weeks

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before diagnosis. Approximately 10^{12} leukemia cell have been estimated to be present by that time *[52]* which indicates that the growing leukemic clone coexisted with normal hematopoiesis for months without any apparent signs of its presence.

1.2 New mutations in leukemic clone as a basis of leukemia progression. Relatively recent experimental evidence suggests that acute myeloid leukemias may originate from multiple clones of malignant cells *[11]*. For chronic lymphocytic leukemia certain genetic events are found in the majority of cells which are considered as 'clonal driver mutations', whereas others, present only in a fraction of the tumor, are deemed to be 'subclonal driver mutations' *[48]*. Sequencing studies revealed about 140 genes that when altered by intragenic mutations can act as driver mutations during tumorigenesis *[51]*. The presence of sub-clonal driver mutations was associated with reduced survival in chronic lymphocytic leukemia *[27]*, and it seems that the degree of sub-clonality might serve as a cancer marker *per se*. Higher diversity is related to a higher mutation rate or longer tumor evolution with more replications *[46]*.

1.3 Possible mechanisms of normal hematopoiesis disruption in leukemia. Interaction between the healthy and cancer cell lines is often described through a competition for physical space resulting in an increased cellular degradation. This is consistent with the observation of an increase of markers for cell death such as lactate dehydrogenase *[5, 14, 25, 47]*. Several mechanisms underlying this spatial competition have been proposed: overcrowding which results in extinction of cells *[20]*; competition for a limited surface niche expressing certain receptors *[6, 53]*; and apoptosis if no contacts to these receptors can be established *[18]*. Other possible mechanisms include induction of cytopenia by impeding hematopoietic stem cells differentiation *[29]* and competition for energy and nutrients *[44]*. Although molecular mechanisms of disruption are not known, at the level of cell populations hematopoiesis disruption is consistent with competitive exclusion principle (also known under several names including Volterra-Lotka Law), which postulates that populations competing for the same limiting resource in one homogeneous habitat cannot coexist long enough *[21, 24]*. However, it is still debatable whether competitive exclusion principle developed for ecosystems can be applied for processes at cellular level.

1.4 Clinical remission and relapse as two states of hematopoiesis in leukemia. The first manifestation of leukemia means not only expansion of leukemic clone into marrow and other organs but also disruption of normal hematopoiesis leading to severe complications of the disease. The goal of induction therapy of leukemia is attainment of a complete remission, which usually requires a period of marrow aplasia, or a “morphologic leukemia-free state,” following induction chemotherapy *[52]*. Complete remission is currently defined as restoration of normal hematopoiesis with a blast cell fraction of less than 5% by light microscopic examination of the bone marrow. This relatively liberal definition reflects the difficulty of identifying leukemic blasts in regenerating marrow by morphologic

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criteria alone. Thus, patients with nearly 5% leukemic blast cells in their marrow specimens can harbor as many as 10^{10} leukemic cells *[7, 41]*. Recurrence of leukemia, called relapse, after therapy is a common problem of leukemias. The goal of post-remission or consolidation therapy is to prolong complete remission by delaying or preventing relapse and to maximize the chance of cure *[52]*. In a typical acute leukemia with chemotherapy the leukemic process is staged strictly as relapse or remission while correlations between the kinetic parameters of the normal and leukemic populations are suggested to characterize the leukemic state *[12]*.

1.5 Spontaneous remission of leukemia. Remission of leukemia without any specific therapy, called spontaneous remission, is an extremely rare and exceptional, relatively well documented but poorly understood phenomenon. Spontaneous remission of acute myeloid leukemia is almost always transient event, with a mean duration in the literature of 7.7 months (range 1–36) *[17]*. In a typical case of spontaneous remission the full restoration of normal hematopoiesis and disappearance of blast cells occur in patient with acute leukemia and concurrent infection *[2, 9, 15, 19, 26, 31, 34, 35, 36, 40, 50]*, blood transfusion *[2, 17, 28, 40, 42]* or cytokine injection *[22, 49]*. The underlying molecular mechanisms of spontaneous remission are still unknown. A potential role of bacterial or fungal infections and blood transfusions was suggested in spontaneous remission occurrence by triggering antileukemic and immune responses *[39]*. Activation of cytotoxic T lymphocytes and macrophages in conjunction with an increased cytotoxicity of Natural Killer cells as well as cytokines of the immune system such as tumor necrosis factor, interferon gamma, and interleukin-2, released during infection may play a role in the occurrence of spontaneous remission *[8, 23, 32, 33, 34]*. However, no clear link between spontaneous remission and infection or immune response was reported in at least one case *[10]*. In another report spontaneous remission was detected after termination of pregnancy *[30]*.

1.6 *Quantitative modelling of leukemia.* Many existing mathematical models describe leukemia without explicit mentioning as a quantitative process of expansion of leukemic clone. This dynamics is described by the Lotka-Volterra equation:

$$\frac{dx}{dt} = rx\left(1 - \frac{x}{K}\right) \tag{1}$$

Here x is the size of the population at a given time, r is mitotic index, and K is the carrying capacity or the maximum amount of cells in bone marrow. A cell population growth will be proportional to the size of the cell population, multiplied on its mitotic index, reflecting proliferation, minus cells leaving the population for whatever reason.

Mechanism of two cell population competition can be taken into account in a system of two equations (2) and (3) with additional coefficients. The Lotka–Volterra equations for logistic population model

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describe dynamics of biological populations x_1 and x_2, competing for some common resource. The formulation in this case can include additional variables α and β to account for their interactions. For leukemia model, α represents the disruptive effect of leukemic clone (x_2) on normal hematopoiesis (x_1) and β represents any effect of normal hematopoiesis on leukemic clone. All α and β-values are supposed to be positive since all interactions are harmful. Also, each cell population can have its own growth rate and carrying capacity. A complete classification of this dynamics is available *[3, 4]*.

$$\frac{dx_1}{dt} = r_1 x_1 \left(1 - \left(\frac{x_1 + \alpha x_2}{K_1}\right)\right) \tag{2}$$

$$\frac{dx_2}{dt} = r_2 x_2 \left(1 - \left(\frac{x_2 + \beta x_1}{K_2}\right)\right) \tag{3}$$

Assuming that competitive Lotka-Volterra dynamics can be used for modelling of leukemia, dynamical system analysis as described in *[38]* might be applied for this purpose. Phase portraits for the system with an additional coefficient reflecting intraspecies competition shows that depending on initial conditions one or another population extinction is inevitable, which is consistent with competitive exclusion principle. For interspecies competition coefficient smaller than the intraspecific one, species coexist is the asymptotic stable state. However, coexistence cannot occur simply as fixed points representing steady species coexistence: the coexisting species should oscillate or display more complex dynamic behavior *[38]*. For leukemia modelling it might represent some slowly progressing chronical variants. Indeed, description of chronical myelogenous leukemia as a process of clonal competition *[43]* and its corresponding model showed that dynamical system of self-renewing and proliferating cell populations might exhibit two main states: (a) a state in which stem cell and blood cell populations fluctuate rapidly which corresponds to acute phase of chronic myelogenous leukemia and (b) hematopoietic stem cells remain at equilibrium and can maintain a stable population level of blood cells, which corresponds to chronic phase *[13]*.

Quantitative models of leukemia are correct within their limits. However, numerical methods are not suited for predicting exact behavior of a nonlinear system beyond a short interval of time which is explained by "butterfly effect" or sensitive dependence on initial conditions [45]. Limitations of quantitative models is not only their approximate descriptions but most importantly the fact that they do not cover all important aspects of leukemia and do not explain the phenomenon of spontaneous remission. Potential risk of using competitive Lotka-Volterra dynamics is explained by the fact that competition mechanism of cell populations in leukemia is not yet proven.

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2 Thermodynamical model of leukemia

Dynamical biological or physical systems display a variety of nonlinear behaviors that can be described by corresponding mathematical models. Despite the diverse nature of processes, resulting mathematical description is quite similar, so it seems possible to understand some aspects of leukemia dynamics with the help of other models. This possibility of common mathematical description will be used to highlight the similarities between leukemia and heat distribution in fluid flows.

Assuming leukemic clone disrupts hematopoiesis and increases its entropy, Lorenz system is suggested to be used for modelling as it reflects a similar process of entropy rising in a uniformly heated shallow layer of fluid. Lorenz found that while being severely truncated version of original Navier-Stokes equations (describing a system with an infinite number of freedom), it still preserves many characteristics of the initial system. Detailed analysis of the Lorenz equations is out of scope of this article, however it is readily available and is widely used as a simplified model of nonlinear system behavior with only three (P, B and R) coupled variable control parameters. Among those three control parameters P and B are considered to be constant and R is a variable. Behavior of the Lorenz system is described in terms of the theory of dynamical systems with definitions for hierarchical stable states or stable phase spaces and conditions of their stability. For an introduction to the theory of dynamical systems see [45].

In brief, Lorenz model for the fluid is the system of three ordinary differential equations:

$$\frac{dx_1}{dt} = -Px_1 + Px_2; \tag{4}$$

$$\frac{dx_2}{dt} = -x_1x_3 + Rx_1 - x_2; \tag{5}$$

$$\frac{dx_3}{dt} = x_1x_2 - Bx_3. \tag{6}$$

Given P=10 and B=8/3 (those are any of constant parameters) the system behavior depends upon R control parameter which reflects heating and relates to entropy increase of the system. For R<1 the origin is the only stable steady state (diagram 1). This situation corresponds to no convection in heating the fluid. At R=1 there are two new stable steady states of the system and a pitchfork bifurcation (a point where a system loses stability). These correspond to steady convection. The system remains stable until R=24.74 (diagrams 2 and 3).

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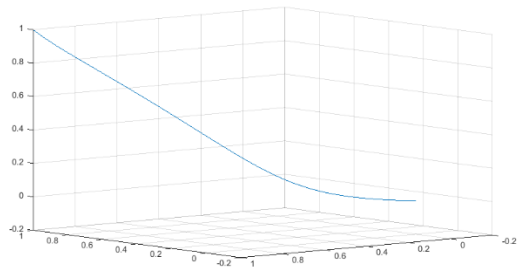

Diagram 1. P=10 and B=8/3 R=1/2

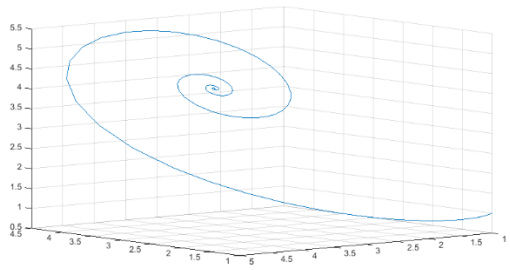

Diagram 2. P=10 and B=8/3 R=5

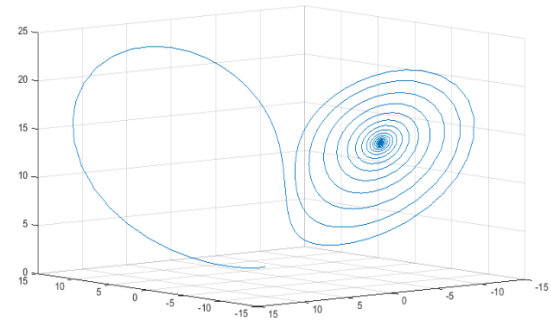

Diagram 3. P=10 and B=8/3 R=15

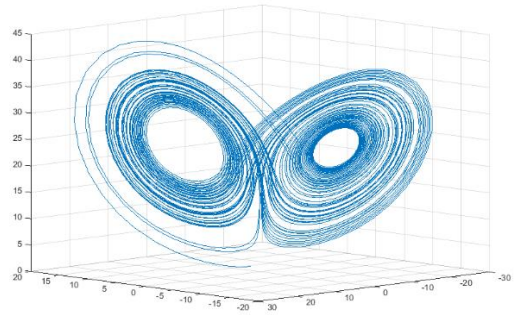

Diagram 4. P=10 and B=8/3 R=25

Diagrams 1-4. Lorenz attractor. From initial steady state (diagram 1) the system compartmentalizes (diagrams 2 and 3) making two new steady states and pitchfork bifurcation. With subsequent entropy increase the system loses stability (diagram 4).

Lorenz found that the system behaves chaotically for P=10, B=8/3 and R>24.74 when it starts with a rotation around one of the focuses with an amplitude increasing with time, thereby forming a divergent spiral. After a number of such oscillations, the system suddenly goes toward the second available focus through a bifurcation. It continues an oscillatory motion around the second available focus along a divergent spiral. After a certain number of oscillations around this focus, the system jumps back to the vicinity of the previous focus, from which it again begins a new divergent oscillatory trajectory (diagram 4) (based on *[37]*).

3. Discussion

Leukemia is an incarnation of chaos. The chaos begins from one or several mutations in cell genome producing independently growing and quickly changing cell population of tumor. At certain moment it starts to affect the functioning of normal hematopoiesis probably competing with it for some common resources or indirectly disrupting its regulatory networks. Degree of disruption or malignancy can vary for different types of leukemias: it is comparatively high for acute leukemias and appears to be

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significantly lower for chronic forms. Degree of malignancy determines survival prognosis for a patient with untreated disease. It is important to make distinction between the tumor *per se* and its disruptive effect on the normal hematopoiesis. If left untreated, a patient will be dying because of failure of normal hematopoietic lineages caused by leukemia cells but not because of presence of leukemic clone. So, we have just came to conclusion that there are two aspects in description of leukemia. Leukemia progression can be defined:

- as a process of tumor growth with acquisition of new properties, including appearance of leukemia sub-clones.
- or as a sequence of events in normal hematopoiesis which greatly influences prognosis for the disease and the fate of a patient.

Obviously, an ideal and complete description of leukemia should include both aspects since we are talking about interconnected processes.

In addition, we have also two methods to describe them: quantitative and qualitative. Quantitative or numerical approach predicts amount of cells in a given cell population over time. For qualitative approach we have to return to definitions of disruption, malignancy or chaos in leukemia. Despite different names and meanings, all three notions can be defined by a thermodynamical parameter of entropy which is commonly understood as a measurement of disorder. It is obvious that leukemia progression is generally a process of entropy rising.

For our modelling purposes we use description of a similar process of entropy rising in a uniformly heated shallow layer of fluid known as Lorenz system. Similarities between two processes are not only entropy rising but also the same starting conditions which are uniform homogenous medium of water in Lorenz system and uniform homogenous medium of marrow in modelling of hematopoiesis in leukemia. In addition, the Lorenz system is ready-to-use and reliable model, studied for more than 50 years.

Graphical solution of ordinary differential equations of Lorenz system is an abstraction which provides three clues for understanding of leukemia. Firstly, at certain level of entropy the system compartmentalizes passing from an only stable state with no convection (diagram 1) to a new steady convection state (diagrams 2 and 3) with two available focuses. In our model of leukemia it reflects appearance of leukemic clone and indicates that in leukemia normal hematopoiesis exists in two qualitatively different states - one state corresponds to remission and another to relapse. In other words, remission and relapse exist as hierarchical stable steady states of hematopoiesis regardless of processes in leukemic clone. Leukemic clone in this context is nothing more than a “heat” source, which initiates and supports described changes. Secondly, there is a pitchfork bifurcation where a system loses stability, between the phase spaces indicating an opportunity of swap between them. Finally, at certain level of

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entropy the system indeed loses stability making possible spontaneous phase space transition through the bifurcation (diagram 4). For our model of leukemia chaotic behavior of Lorenz system (when it randomly swaps between two different states $x(t)>0$ and $x(t)<0$) corresponds to unexpected events in leukemia, such as spontaneous remission. In this model spontaneous remission can be described as transition from relapse steady state to remission steady state of normal hematopoiesis through a bifurcation. Concurrent infection, blood transfusions, cytokine injections could be considered as factors contributing to stability loss and thus facilitating the spontaneous states transition. Remission is usually short in spontaneous remission since leukemic clone prevails.

Another possible symmetrical scenario of spontaneous states swap is relapse of leukemia. It involves reaching of bifurcation point by hematopoiesis in the state of remission. Spontaneous remission and "spontaneous relapse" are the two symmetrical facets of the same process of the phase spaces transition through a bifurcation.

As previously mentioned, successful course of chemotherapy should result in a period of marrow aplasia, or a "morphologic leukemia-free state," which might correspond to bifurcation. The role of chemotherapy in leukemia is dual. It is not limited only to eradication of leukemic clone. Chemotherapy might also play a hematopoietic regulatory role driving hematopoiesis to bifurcation and making possible states swap. By going further one can suggest that excessively high doses of chemotherapy in consolidation may induce relapse by the same mechanism.

Cytopenia observed at the first manifestation of leukemia can be interpreted as an adaptive reaction of hematopoiesis to entropy increase caused by leukemic clone [1]. It would be easier to explain this idea by operating the term "internal energy". Since internal energy in thermodynamics is a function of entropy this substitution is adequate. With appearance of leukemic clone in marrow and subsequent increase of its internal energy, normal hematopoiesis maintains homeostasis of the whole system, decreasing its own internal energy. The latter leads to stem cell proliferation and differentiation rate decrease and results in cytopenia. So, the normal hematopoiesis is suppressed in leukemia by normal negative feedback loop which regulates hematopoiesis physiologically.

Based on the model, some hypotheses (a, b and c) about leukemia behavior can be formulated. Definition of remission solely through the state of normal hematopoiesis leads to the following: (a) percentage of leukemia cell in marrow for relapse or remission criterion is not strict cut-off constant but a variable value [1]; (b) probability of getting remission depends upon reaching bifurcation; (c) length of remission depends upon degree of eradication of leukemia cells in induction therapy.

All three hypotheses can be tested in laboratory and by statistical analysis, however refinement of the model appears to be more difficult. Presumably, it should include integration of both quantitative and qualitative aspects of leukemic clone and normal hematopoiesis interaction. The model verification

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would also require development of methods for entropy assessment in cell populations on laboratory models and in humans. Since the entropy in the thermodynamical model is proportional to α-coefficient of equation (2) for Lotka-Volterra competitive dynamics in cell populations, entropy change over short interval of time can be mathematically defined through numerical variables of the same equation. *In vitro* entropy changes in cell populations could be assessed by growing cell cultures on chemically defined media and by monitoring chemical composition of media *vs* processes in cells.

Providing equations for Lorenz system of heat distribution in water give correct description of leukemia the following metaphoric conclusion seems appropriate: "Leukemia is fire in blood".

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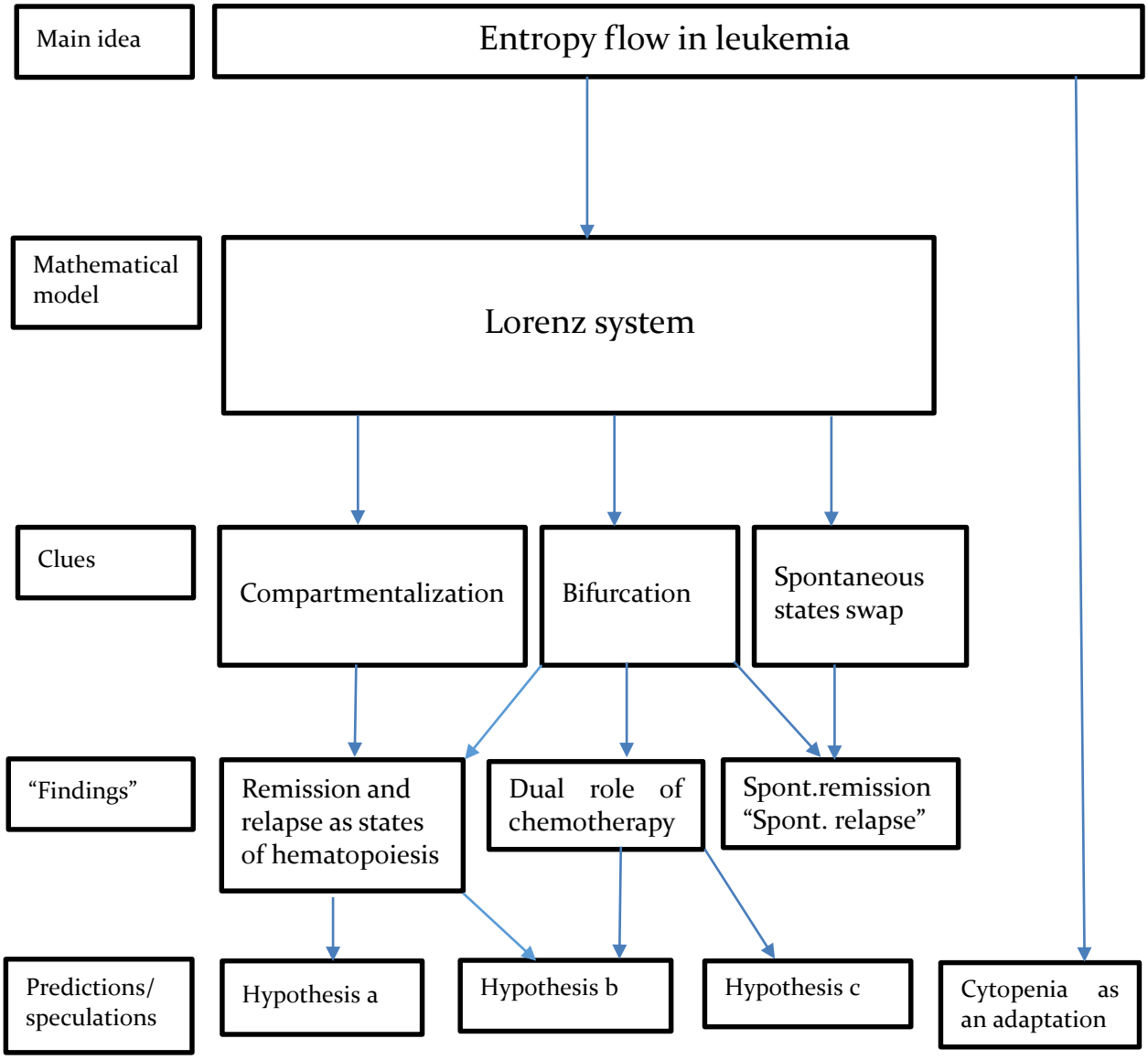
ASSOCIATED CONTENT

Structural diagram of major ideas in the article.



Not all connections are shown.

The article in one sentence:

"Remission and relapse are states of normal hematopoiesis but not percentage of blasts".

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MATLAB simulation scirpt for the Lorenz System equations in the time interval [0,100] with initial conditions [1,1,1].

```
clc
p=10;
b=8/3;
r=1/2;
f = @(t,a) [-p*a(1) + p*a(2); r*a(1) - a(2) - a(1)*a(3); -b*a(3) + a(1)*a(2)];
[t,a] = ode45(f,[0 100],[1 1 1]);
plot3(a(:,1),a(:,2),a(:,3))
```

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