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DEZVOLTAREA UNUI MODEL DE HEMATOPOIEZĂ CLONALĂ

Etapa 4

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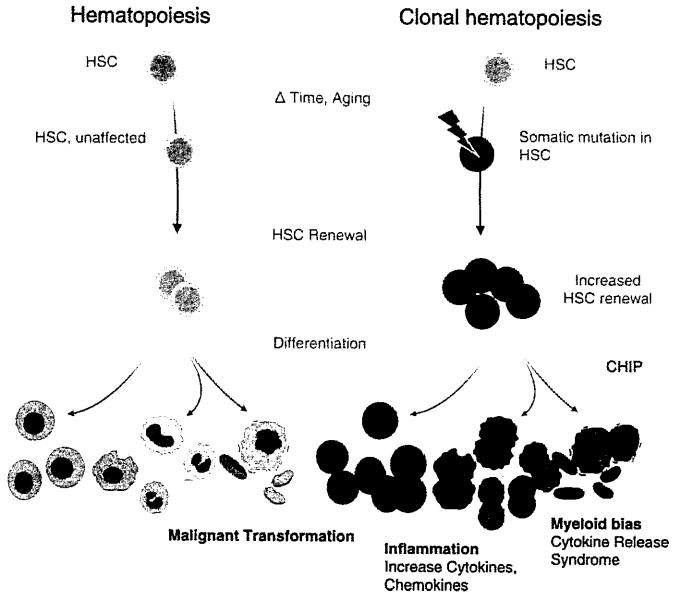
INTRODUCERE – hematopoieza clonală

În cazul hematopoiezei clonale, o singură celulă sau o mică populație de celule stem hematopoietice dobândește modificări genetice sau epigenetice care conduc la o proliferare necontrolată și la formarea unei clone distincte. Acest fenomen poate duce la apariția unei variate game de afecțiuni, inclusiv malignități hematologice, ca și leucemia cronică mieloidă.



Von Bonin, M., Jambor, H.K., Teipel, R. *et al.* Clonal hematopoiesis and its emerging effects on cellular therapies. *Leukemia* **35**, 2752–2758 (2021).

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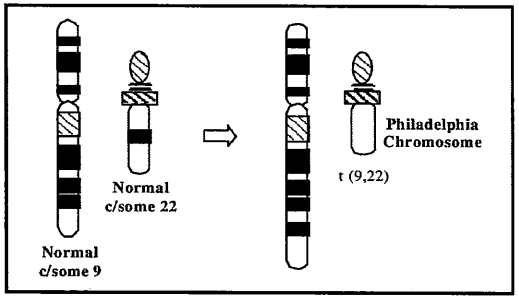
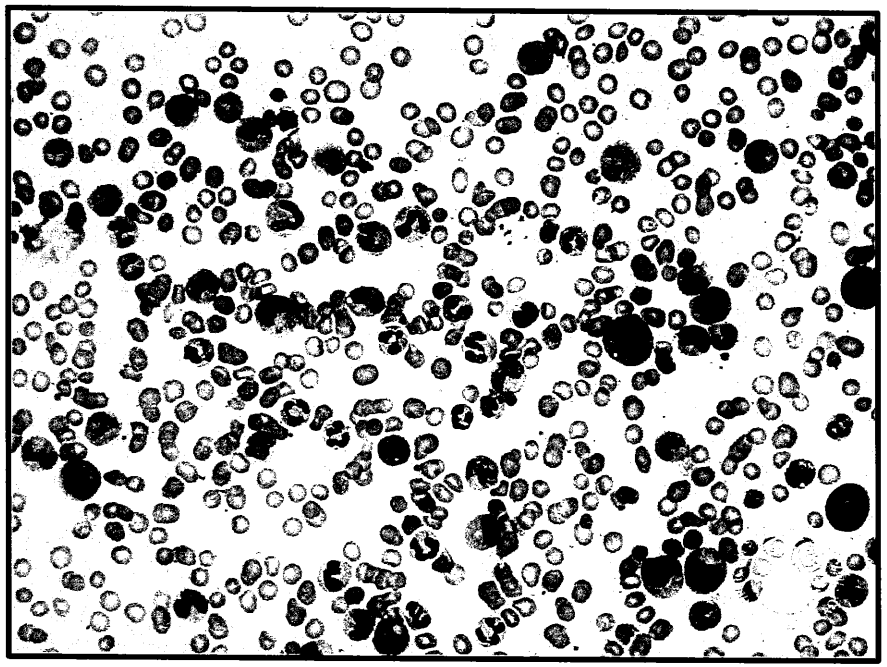
INTRODUCERE – leucemia cronică mieloidă

Leucemia cronică mieloidă reprezintă o afecțiune hematologică malignă caracterizată prin proliferarea excesivă și anormală a celulelor mieloide în măduva osoasă, sânge periferic și alte țesuturi hematopoietice. Această formă de leucemie face parte din categoria bolilor mieloproliferative cronice, având un curs evolutiv mai lent în comparație cu alte tipuri de leucemii. Un aspect definitoriu al leucemiei cronice mieloide este prezența cromozomului Philadelphia, rezultat dintr-o translocație între cromozomul 9 și 22.





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OBIECTIVUL STUDIULUI

modelarea matematică a hematopoiezei clonale în contextul leucemiei cronice mieloide

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REZULTATE PRELIMINARE

- elaborarea unui model de bază matematic de proliferare a celulelor leucemice in raport cu celulele hematopoietice normale ș pentru descrierea dinamicii celulare în compartimentul celulelor primitive stem

$$\begin{cases} x'(t) = \frac{ax(t)}{1+b_1x(t)+b_2y(t)} - cx(t) \\ y'(t) = \frac{Ay(t)}{1+B(x(t)+y(t))} - Cy(t) \ . \end{cases} \tag{1}$$

Here, $x(t)$ and $y(t)$ represent the populations of normal and abnormal/leukemic hematopoietic stem cells at time t, respectively. The parameters a and A correspond to the growth rates, while c and C signify the cell death rates or apoptosis rates. Additionally, the sensitivity parameters b_1, b_2, and B play a crucial role in governing the self-regulation process. It is assumed that, for both stem cell populations, the growth rate exceeds the death rate, denoted as $a > c$ and $A > C$. Furthermore, the relative advantage of leukemic stem cells, characterized by their reduced sensitivity to the bone marrow microenvironment compared to normal stem cells, is expressed through the relationships $b_1 \geq b_2 > B$.

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- pornind de la modelul de bază s-a elaborat un model matematic complex de evoluție clonală în leucemia mieloidă cronică care să ia în considerare toate elementele de hematopoieză incluzând constante separate pentru diviziune simetrică/asimetrică, diferențiere granulocitară, apoptoză, luând în considerare și starea activă/inactivă a celulelor stem normale/leucemice.

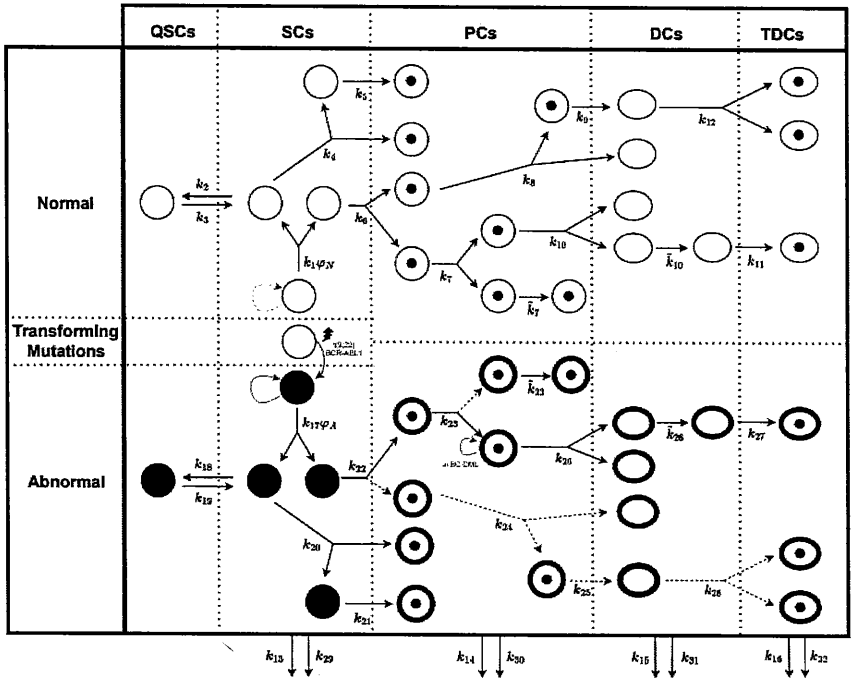

Figure 1: The proposed model is represented using compartments, where a specific rate constant influences each cellular event denoted as k_j. Both normal and abnormal stem cells (NSCs/ASCs) possess the ability to self-renew, which is indicated by the rate constants multiplied by the corresponding self-regulatory functions $(k_1\varphi_N)/(k_{17}\varphi_A)$, respectively. Additionally, they can enter a resting phase with rate constants $(k_2)/(k_{18})$, during which they become normal/abnormal quiescent stem cells (NQSCs/AQSCs). After a period of time, the quiescent stem cells can reactivate, denoted by rate constants $(k_3)/(k_{19})$, and return to an active state as normal/abnormal cycling stem cells. The normal/abnormal cycling stem cells can give rise to intermediate normal/abnormal progenitor cells (NPCs/APCs) through asymmetric $(k_4)/(k_{20})$ division and symmetric $(k_6)/(k_{22})$ differentiation. Additionally, they can undergo direct differentiation $(k_5)/(k_{21})$ into intermediate normal/abnormal progenitor cells. These intermediate normal/abnormal progenitor cells, in turn, can proliferate and give rise to mature normal/abnormal progenitor cells (NPCs/APCs) through symmetric $(k_7)/(k_{23})$ and asymmetric $(k_8)/(k_{24})$ divisions. Similarly, they can give rise to normal/abnormal differentiated cells (NDCs/ADCs) through asymmetric $(k_8)/(k_{24})$ division. Normal/abnormal mature progenitor cells can directly differentiate $(\widetilde{k}_7)/(\widetilde{k}_{23})$ into other types of mature normal/abnormal progenitor cells. Additionally, they can undergo direct differentiation $(k_9)/(k_{25})$ into normal/abnormal differentiated cells, and they can give rise to normal/abnormal differentiated cells through symmetric $(k_{10})/(k_{26})$ differentiation. The normal/abnormal differentiated cells can undergo direct differentiation $(\widetilde{k}_{10})/(\widetilde{k}_{26})$ into other types of normal/abnormal differentiated cells. Furthermore, they can give rise to normal/abnormal terminally differentiated cells (NTDCs/ATDCs) through direct $(k_{11})/(k_{27})$ and symmetric $(k_{12})/(k_{28})$ differentiation. Each cell type, except for quiescent stem cells, whether normal or abnormal, has a death rate represented by the rate constants $(k_{13})/(k_{29})$ for cycling stem cells, $(k_{14})/(k_{30})$ for progenitor cells, $(k_{15})/(k_{31})$ for differentiated cells, and $(k_{16})/(k_{32})$ for terminally differentiated cells.

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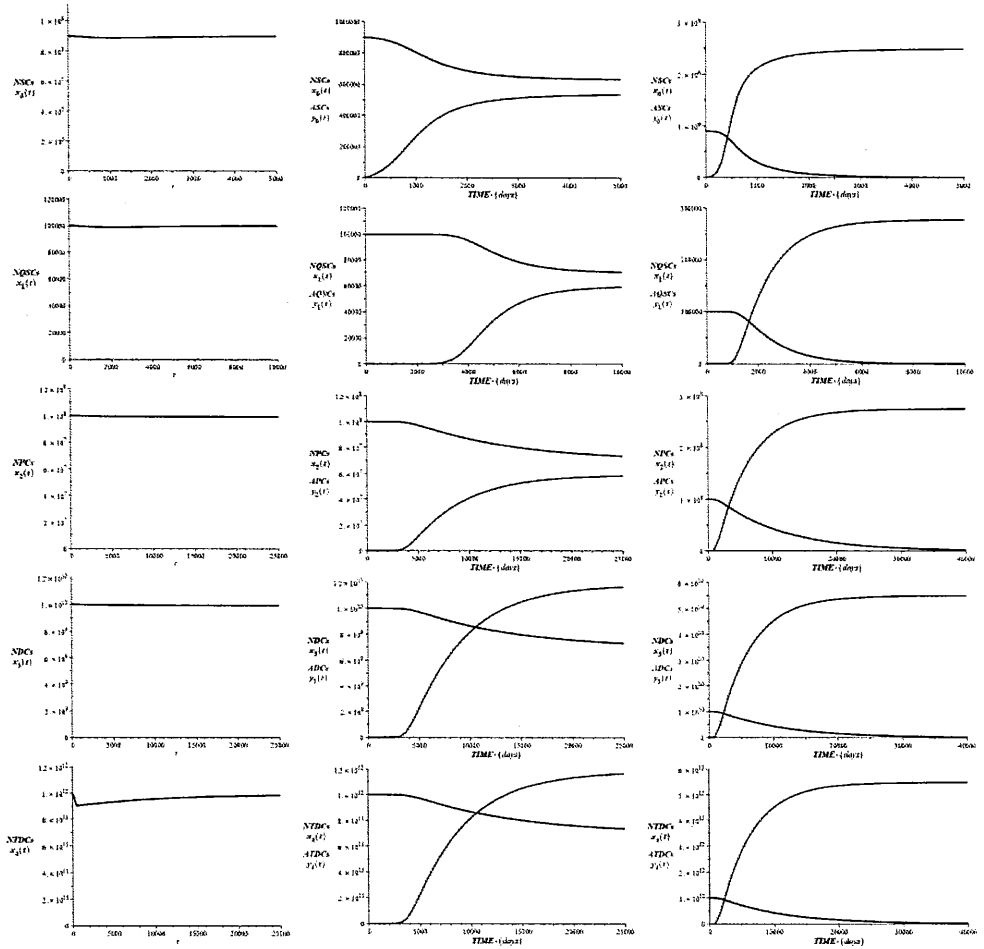
Leucemia cronică mieloidă prezintă trei faze clinice, cea cronică cu evoluţie lentă, cea accelerată şi acută sau blastică care se comportă asemenea unei leucemii acute mieloide.

→ elaborarea unui model de hematopoieză clonală care să simuleze aceste faze ale leucemiei



(a) Normal state (b) Chronic phase (c) Accelerated-acute phase

Figure 3: Behavior of normal and abnormal (leukemic) cell populations. Initial conditions: (a) normal cell populations: cycling stem cells $x_0(0) = 9\times10^5$, quiescent stem cells $x_1(0) = 10^5$, progenitor cells $x_2(0) = 10^8$, differentiated cells $x_3(0) = 10^{10}$, terminally differentiated cells $x_4(0) = 10^{12}$; (b) - (c) normal and abnormal cells: cycling stem cells $x_0(0) = 9 \times 10^5$ and $y_0(0) = 1$, quiescent stem cells $x_1(0) = 10^5$ and $y_1(0) = 1$, progenitor cells $x_2(0) = 10^8$ and $y_2(0) = 1$, differentiated cells $x_3(0) = 10^{10}$ and $y_3(0) = 1$, terminally differentiated cells $x_4(0) = 10^{12}$ and $y_4(0) = 1$.

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DISEMINAREA REZULTATELOR

A Mathematical Model of Cloned Hematopoiesis Explaining Phase Transition in Myeloid Leukemia

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Abstract: This study presents a mathematical model describing cloned hematopoiesis in chronic myeloid leukemia (CML) through a nonlinear system of differential equations. The primary objective is to understand the progression from normal hematopoiesis to the chronic and accelerated-acute phases in myeloid leukemia. The model incorporates intrinsic cellular division events in hematopoiesis and delineates the evolution of chronic myeloid leukemia into six compartments: cycling stem cells, quiescent stem cells, progenitor cells, differentiated cells, and terminally differentiated cells. Our analysis reveals the existence of three distinct steady states within the dynamical system, representing normal hematopoiesis, the chronic phase, and the accelerated-acute stage of the disease. We investigate the local and global stability of these steady states and provide a characterization of the hematopoietic states based on this analysis. Additionally, numerical simulations are included to illustrate the theoretical results.

Keywords: mathematical modeling; dynamical system; steady state; stability; cloned hematopoiesis; chronic myeloid leukemia; cycling stem cells; quiescent stem cells; progenitor cells; differentiated cells; terminally differentiated cells; pseudo-chemical reactions

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