Journal of Kerman University of Medical Sciences

JKMU

Journal of Kerman University of Medical Sciences, 2017; 24(3): 229-236

Diagnosis of B-CLL Leukemia Using Fractal Dimension

Tohid Yousefzadeh Hassanluie, M.Sc.[1], Mohammad Reza Rezaie, Ph.D.[2], Zahra Rostami, M.Sc.[3]

1- Department of Nuclear Engineering, Faculty of Electrical Engineering, Graduate University of Advanced Technology Kerman, Iran

2- Assistant Professor, Department of Nuclear Engineering, Faculty of Electrical Engineering, Graduate University of Advanced Technology Kerman, Iran (Corresponding author; E-mail: mr.rezaie@kgut.ac.ir)

3- Ph.D. Medical student, Kerman University of Medical Sciences, Kerman, Iran

Received: 1 May, 2016 Accepted: 12 April, 2017

ARTICLE INFO

Article type:
Original article

Keywords:
Fractal Dimension
Predict
Detect
CLL Blood Cancer
Box Counting

Abstract

Background: Leukemia is cancer of blood and bone marrow cells. In general, there are four types of leukemia: chronic myelogenous leukemia (CML), acute myeloid leukemia (AML), B-cell chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL). Fractal geometry can be introduced as one of the effective ways to detect this type of cancer. In this study, with introducing an effective method, it is tried to predict CLL cancer through the measurement of nucleus cell fractal dimension.

Methods: Blood samples of 30 healthy individuals and 30 patients with blood cancer were taken and digital pictures were taken from the samples with 100X optical microscope. Finally, nucleus cells fractal dimension was calculated with box counting method and the obtained data were analyzed through statistical software.

Results: Mean fractal dimension of lymphoma type B cell was 1.367± 0.0011 in healthy subjects and 1.398 ± 0.0016 in cancer patients. The difference between healthy cells and cancer cells fractal dimension is significant.

Conclusion: Fractal dimension measurement can be used to screen cancer cells from healthy cells. The detection point for identification of CLL cancer by fractal dimension method was introduced as 1.3 (the middle point of normal cells and cancer cells fractal dimension). In the case of blood cell fractal dimension higher than 1.383, the patient is suspected to have CLL blood cancer.

Citation: Yousefzadeh Hassanluie T, Rezaie M.R, Rostami Z. Diagnosis of B-CLL Leukemia Using Fractal Dimension. Journal of Kerman University of Medical Sciences, 2017; 24(3): 229-236.

Introduction

In leukemia, bone marrow produces a lot of abnormal white blood cells (1). These cells stop the production of white blood cells. Leukemia cells also affect the production of red blood cells and platelets. One of the four most common cancers in children is leukemia (2). Leukemia is divided into two categories of acute and chronic leukemia (3, 4). In general, there are four types of leukemia: chronic myelogenous leukemia (CML), acute myeloid leukemia (AML), B-cell chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL). Chronic myelogenous leukemia is a type of blood cancer that affects bone marrow cells and has a chronic process (5, 6). Acute myeloid leukemia affects bone marrow cells (7). Acute lymphoblastic leukemia affects lymphoid cells and finally B-cell chronic lymphocytic leukemia is a blood cancer of the lymph cells or lymphocytes that make up lymphoid tissues and has a chronic process. In chronic leukemia, neoplastic cells appear to be mature but they are not entirely normal and cannot fight infections. Chronic lymphocytic leukaemia (CLL) is a type of slow growing leukaemia that affects developing B-lymphocytes (also known as B-cells).These cells are specialized white blood cells. Under normal conditions they produce immunoglobulins (also called antibodies) that protect our bodies against infection and disease. In people with CLL, lymphocytes undergo a malignant (cancerous) change and become leukaemic cells (8, 9). B-CLL is the most common type of leukemia in Europe and around 40 percent of adults over the age of 60 years have leukemia (10, 11). The main cause of the disease is unknown (12, 13), and it is more prevalent in farmers (13, 14). The clinical course of the disease is varied and its diagnosis is usually based on classical parameters suggested by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) and the National Cancer Institute (NCI); accordingly, more than 5×109 per liter cells with small lymphocytes, despite normal appearance, and specific Immunophenotyping show CLL cancer (15, 16). Fractal geometry can be used as an effective method to detect and anticipate the type of cancer. The Scientists have come to recognize that many natural constructs in medical sciences are better characterized using fractal geometry. Some uses of fractal geometry are in medical fields such as molecular biology, pathology of tumor, bone pathology, vascular pathology, neuropathology, corneal ulcers of each post simplex, different regions of heterochromatin and Chromatin in the cell nucleus and etc (17, 18)

The importance of chaos theory Suffices to say that this theory with relativity theory and quantum mechanics in the twentieth century are known as three major scientific progresses.

Chaotic geometry History

The term fractal means an irregular shaped stone meant to be broken. Figure 1 shows an example that looks irregular, but a closer look shows that it is formed of smaller parts which are more or less similar to the whole and called self-similar patterns.

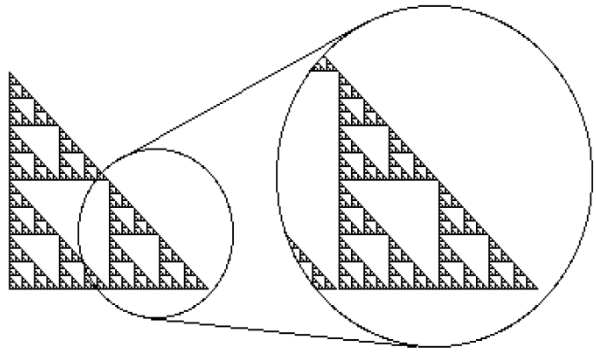


Figure 1. An example of self-similar pattern

Fractal traits are the most unpredictable ones in their behavior. Fractal is chaos in space and has dimensions with non-integer values. The analysis of these structures requires the special theory. Today, with the introducing of chaos theory and analysis of dynamic phenomena, the investigation of chaotic behavior of nature in different branches of science are possible. There are two approaches in the analysis of chaos in biological systems. Some believe that biological systems have normal and regular behavior and others believe that some biological examples are chaos.

The fractal dimension of cells in the blood system can be used to diagnose CLL cancer. In this study, the basic assumptions taken into account were as follow: 1- Cancer affects blood cells, 2 – Cancer Changes the Lymphocytes form, 3 - Cancer cell surface of the lymphocytes is chaotic, 4 - Leukemia fractal dimension increases with the cell nuclei deformation and 5 – Fractal is a prediction method for the detection of blood cancer.

By doing this research, it was tried to examine the validity of the initial assumptions.

There has been already extensive use of fractal geometry in medical researches and some examples are mentioned here.

James W. Baish et al. used fractal geometry in their cancer research (19). Naeim F et al studied the fractal spatial patterns in 31 samples of bone marrow cancer. (20). Dey et al measured the fractal dimension of cytology smears using breast imaging by box counting method (21). Ohri et al, by measuring the fractal dimension of benign and malignant cervical cells, identified a significant difference in the fractal dimension, and introduced this method as an auxiliary tool in the differentiation of benign and malignant cells (22).

Simon S. Cross, in a study on colorectal polyps, observed that polyps had a statistically significant difference in their average fractal dimension (17). Dey et al. studied the fractal dimension of glands in simple hyperplasia, atypical complex and endometrial carcinoma (23) B. Ilkhanizadeh et al. studied nucleus boundary of cancer cells in urine cytology (24). Ravanshadi S et al used fractal and chaos theory in biomedical engineering. In the analysis of heart beat signal for normal and CHF (congestive heart failure) patients, fractal dimension method was used as a qualifier. They were observed that the fractal characteristic of heart beat signal in normal subjects had a multifractal form, while in patients it had a monofractal form. Chaotic parameters of ECG signal was calculated in three different groups of VT (ventricular tachycardia) patients, VF (ventricular fibrilation) patients and one group of normal subjects.They showed that healthy coronary arteries express a fractal behavior, while in totally blocked coronary artery patients, there is no evidence of fractal phenomenon (25).

As it is seen, the term fractal is a notion quite familiar for medical researchers.

Method

To evaluate the validity of the assumptions, cytology slides of blood samples of 30 healthy subjects and 30 people with leukemia in Shahid Bahonar hospital in Kerman were randomly selected and numbered. Then, they were studied with Olympus optical microscope at 100X magnification .A sample of these images is shown in Figure 2.

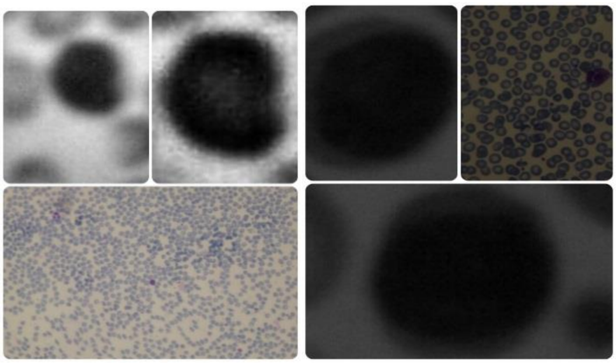


Figure 2. A sample of blood cytology slide

The fractal dimensions of the blood cells images were calculated using appropriate fractal software. Five different boxes with dimensions of 8 × 8, 12 × 12, 16 × 16, 20 × 20 and 24 × 24 pixels were applied on healthy and cancer cell images and fractal dimension is obtained by box counting method .The fractal dimensions were processed by statistical software.

After applying a box with different pixels to the cell image, the fractal dimension was calculated using Equation 1(26):

$$y = A.X^{-D} \quad (1)$$

Where D is the fractal dimension, y is boxes that occupied by the nucleus of a particular cell, X is the pixels dimension and A is a constant factor.

An example of grid cells is shown in Figure 3.

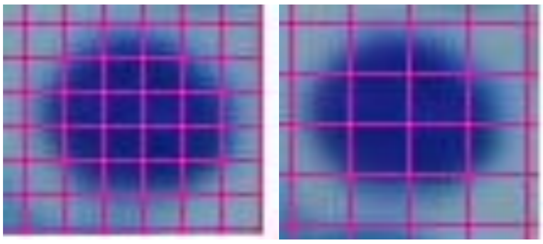


Figure 3. Sample of box that applied on blood cells

The numbers of occupied boxes based on different pixel sizes are shown in Table 1 and Figure 4.

Table 1. Number of occupied boxes versus pixel size

The Pixel of box	8	12	16	20	24	28	32
The number of occupied boxes	24	13	10	8	6	4	4

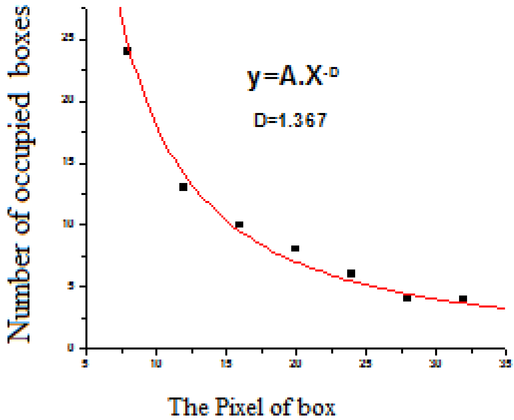


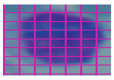
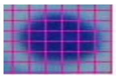
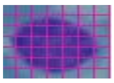
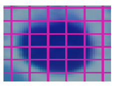
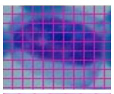
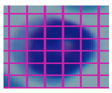
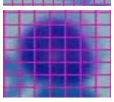
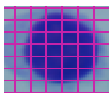
Figure 4. The y=A.X-D behavior of result with D=1.367

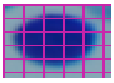
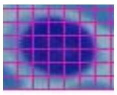
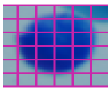
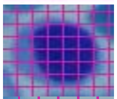
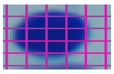
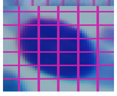
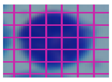
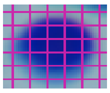
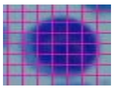
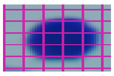
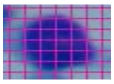
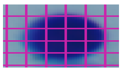
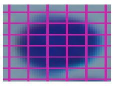
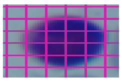
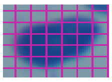
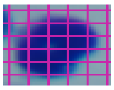
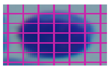
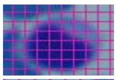
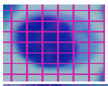
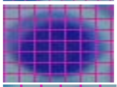
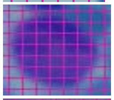
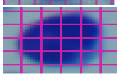
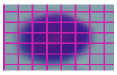
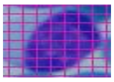
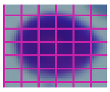
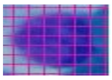
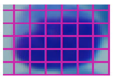
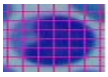
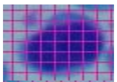
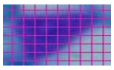
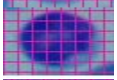
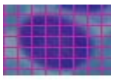
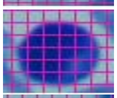
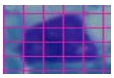
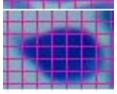
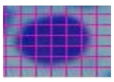
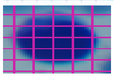
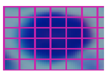
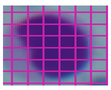
Figure 4, shows a curve that fitted on result with $y = A.X^{-D}$ format according to the Equation 1. After this process, the fractal dimension of sample was about 1.367.

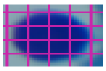
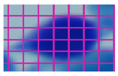
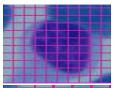
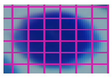
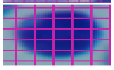
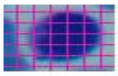
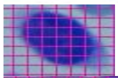
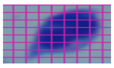
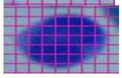
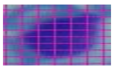
Results

In determining the fractal dimension, the above mentioned steps were done for 60 samples and the obtained results have been shown in Table 2.

Table 2. The fractal dimension of 60 samples of normal and cancer blood cells

sample	**Di'fractal dimension cancer cells**		**Difractal dimension normal cells**	
1		1.395		1.369
2		1.398		1.367
3		1.399		1.365
4		1.398		1.366

5		1.399		1.367
6		1.398		1.368
7		1.397		1.369
8		1.397		1.367
9		1.399		1.365
10		1.399		1.367
11		1.398		1.366
12		1.395		1.367
13		1.398		1.368
14		1.396		1.366
15		1.395		1.367
16		1.395		1.368
17		1.398		1.367
18		1.395		1.369
19		1.395		1.367
20		1.395		1.367
21		1.398		1.367
22		1.399		1.367
23		1.398		1.367
24		1.395		1.369

25		1.397		1.367
26		1.397		1.368
27		1.398		1.367
28		1.395		1.368
29		1.398		1.367
30		1.398		1.365
Mean and error	$\bar{D}$ cancer = 1.398 ± 0.001592		$\bar{D}$ normal = 1.367 ± 0.001096	

In this table, Di ', Di, D, and D' are the fractal dimensions of cancer cells, normal cells, and average fractal dimension of cancer cell, and healthy cells respectively. At the bottom of the table, the $\sigma Ds = \sqrt{\frac{\sum\left(Di - \bar{D}\right)}{30}}$ is the sample standard deviation. Finally, the middle fractal dimension (Dm) of cancer and healthy cells is obtained using the equation (2):

$$Dm = \left|\frac{D_{normal} - D_{cancer}}{2}\right| \qquad (2)$$

The average fractal dimension (Dm) is introduced in order to detect and predict CLL blood cancer. In the case of fractal dimension of blood cells lower than the Dm, the person is healthy and larger amounts of Dm show a risk for cancer.

Discussion and conclusion

Mean fractal dimension of healthy and cancer cell samples were respectively 1.367 ± 0.0011 and 1.398 ± 0.0016 and showed significant difference. Fractal dimension measurement, provided that it is done purposefully and with scientific principles, can be used in the detection of cancer cells and differentiation of them from healthy cells. Mean fractal dimension of healthy and cancer blood cells (1.367+1.398)/2=1.383) can be introduced as a reference level for the B-CLL cancer diagnosis. If the fractal dimension of a blood cell sample is greater than the reference level (1.383), then the person is diagnosed with leukemia and otherwise, B-CLL cancer risk is low

Acknowledgements

The authors would like to appreciate Hematology Department of Shahid Bahonar Hospital, Kerman, Iran and cooperation of Dr. Jahanbanu Shahriari and Dr. Fatemeh Nabipour.

References

1. Murray M, Rushworth S, Macewan D. Micro rnas as a new therapeuti target towards leukaemia signalling. *Cell Signal* 2012; 24(2): 363-8.

2. Ferrara F, Schiffer CA. Acute myeloid leukaemia in adults. *Lancet* 2013;381(9865): 484-95.

3. National Cancer Institute. What you need to know about lukemia. U.S. Department of Health and Human Services: National Institutes of Health; 2013. P.1-30.

4. Hideshima T, Mitsiades C, Tonon G, Richardson PG, Anderson KC. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. *Nat Rev Cancer* 2007; 7(8): 585-98.

5. National Institute for Clinical Excellence (NICE). Guidance on the use of imatinib for chronic myeloid leukaemia. National Institute for Clinical Excellence; 2003. P.1-21.

6. Lewandowski K, Gniot M, Lewandowska M, Wache A, Ratajczak B, Czyż A, et al. B-Cell chronic lymphocytic leukemia with 11q22.3 rearrangement in patient with chronic myeloid leukemia treated with imatinib. Case Rep Med 2016; 2016: 9806515.

7. Estey E, Döhner H. Acute myeloid leukaemia. Lancet 2006; 368(9550): 1894-907.

8. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. Eur J Health Econ 2013; 14(5):749-59.

9. Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. Health Technol Assess 2016; 20(26): 1–48.

10. Kokhaei P, Rezvany M, Virving L, Choudhury A, Rabbani H, Osterborg A, et al. Dendritic cells loaded with apoptotic tumour cells induce a stronger T-Cell response than dendritic Cell-tumour hybrids in B-Cll. Leukemia 2003; 17(5): 894-9.

11. Maloney DG. Anti-CD20 antibody therapy for B-cell lymphomas. *N Engl J Med* 2012; 366: 2008–16.

12. Adami J, Gridley G, Nyren O, Dosemeci M, Linet M, Glimelius B, et al. Sunlight and non-hodgkin's Lymphoma: a population-based cohort study in Sweden. Int J Cancer 1999; 80(5):641-5.

13. Goldin LR, Pfeiffer RM, Li X, Hemminki K. familial risk of lymphoproliferative tumors in families of patients with chronic lymphocytic leukemia: results from the Swedish family cancer database. *Blood* 2004;104(6):1850-4.

14. Flodin U, Fredriksson M, Persson B, Axelson O. chronic lymphatic leukaemia and engine exhausts, fresh wood, and Ddt: a case-referent study. *Br J Ind Med* 1988; 45(1):33-8.

15. Herishanu Y, Polliack A. chronic lymphocytic leukemia: a review of some new aspects of the biology, factors influencing prognosis and therapeutic options. *Transfus Apher Sci* 2005; 32 (1):85-97.

16. Jain N, O'Brien S. Initial treatment of CLL: integrating biology and functional status. *Blood* 2015;126(4):463-70.

17. Cross SS. Fractals in Pathology. *J Pathol* 1997; 182(1): 1-8.

18. Baish JW, Jain RK. Fractals and Cancer. *Cancer Res* 2000; 60(14): 3683-8.

19. Naeim F, Moatamed F, Sahimi M. Morphogenesis of the bone marrow: fractal structures and diffusion limited growth. *Blood* 1996; 87(12): 5027-31.
20. Dey P, Mohanty SK. fractal dimensions of breast lesions on cytology smears. Diagnostic Cytopathol 2003; 29(2):85-6.
21. Ohri S, Dey P, Nijhawan R. Fractal dimension in aspiration cytology smears of breast and cervical lesions. Anal Quant Cytol Histol 2004; 26(2):109-12.
22. Dey P, Rajesh L. Fractal dimension in endometrial carcinoma. Anal Quant Cytol Hisol 2004; 26(2):113-6.
23. Noroozinia F, Behjati G, Shahabi S, Islamlo HF, Mohammad Hassan Z, Ilkhanizadeh B. Fractal study on nuclear boundary of cancer cells in urinary smears. *Urmia Medical Journal* 2009; 20(2):104-110, [In Persian]
24. Samin L. healthy and sick heart beat signal analysis using fractal. *Eleventh Conference of Medical Engineering* 1382 [In Persian]
25. Rezai F.sweet, fractals and chaos of Medical Sciences.Applied Mathematics,*University of Shiraz*, 1391 [In Persian]
26. Hideki T. Fractals in the Physical Sciences. Manchester University Press; 1990. 141-2.