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Natural frequency of cancer cells as a starting point in cancer treatment

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Breast cancer and prostate cancer are the most common gender-specific types of cancer among women and men respectively, around the world. The most preferred treatment embraced by the patients is chemotherapy. The anticancer drugs developed and used so far cannot completely cure cancer at all stages and also exhibit some side effects in the patients who undergo chemotherapy. Besides this, some cancer cells eventually acquire resistance to many drugs and evade the treatment procedures. All these factors play a vital role in persuading the researches to find alternative modes of treatment for cancer. This communication proposes an unconventional mode of cancer treatment by determining the natural frequencies of normal and cancer cells. By utilizing these frequencies, it is possible to kill the cancer cells specifically, sparing the healthy cells. The normal and cancer cells in case of breast (MCF-10A, MCF-7) as well as prostate cancer (BPH, LNCap) are modelled as a sphere in ANSYS. The modal analysis is done in order to obtain their natural frequencies along with their mode shapes at different frequencies. The results show that the natural frequency of the normal cells is much higher than that of the cancer cells at each corresponding mode. The natural frequency is proportional to the mechanical properties of the cells and is insignificant with respect to the change in diameter of the cells. Thus, utilizing the natural frequency, cancer cells may be specifically targeted while the burdens of chemotherapy and drug resistance.

Keywords: Breast cancer, modal analysis, natural frequency, prostate cancer.

CANCER cells divide uncontrollably and grow rapidly, forming malignant tumours as well as invading nearby organs of the body. Cancer can also spread to more distant parts of the body through the lymphatic system or bloodstream. According to the American Cancer Society (ACS), a total of 1,658,370 new cancer cases and 589,430 cancer deaths were projected to occur in the United States

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in 2015 alone[1]. The cancer cells develop multidrug resistance (MDR) during chemotherapy, which is a major stumbling block for cancer treatment[2]. The two most common invasive cancers that occur in men and women are prostrate and breast cancer respectively. They lead the estimated new cases of cancer identified in 2015 (ref. 1). Although these cancers develop in two different organs which are diverse in their structure and function, both organs need gonadal steroids for their growth and consequently their tumours are hormone-dependent and have some similarities[3]. Despite the various conventional treatments in practice, there is constant search for other modes of treatment which have less side-effects.

Every physical system in the universe is set to vibrate. Vibration is a mechanical phenomenon whereby oscillations occur about an equilibrium point[4]. Since all physical systems have a unique mass, spring constant and damping coefficient, each system has a specific resonant natural frequency. The natural frequency of an object is the rate at which it vibrates when it is not disturbed by an external force. In case of humans, every organ in the body and even every cell has a resonant natural frequency, and this is a result of the characteristics of the particular physical system parameters. Moreover, the complex body will vibrate in different ways and each vibrating mode will have its own frequency of oscillation. The shape of vibration is complicated and changes from one instant to the next.

In order to distinguish many of the complexities of living organisms, it is necessary to understand the behaviour of a cell, as it is the basic unit of all living organisms[5]. Each organ has a specific function whose performance is governed by a vast spectrum of biomechanical and biochemical processes taking place at the cellular level. The mechanical properties of biological cells could provide information about the healthy state of the organism, since some of the biological functions are governed by the cellular mechanical properties. Shape, size and stiffness of the cells are some of the major properties, which influence their health status. However, these mechanical properties of individual cells are altered in diseased state. For example, the increased stiffness of the red blood cells affects the normal flow of blood in the small capillaries[6].

The natural frequency of the cells is generally obtained by geometric configurations, such as spheres, ellipses, etc. The free vibration of solid and hollow spheres has been the subject of study for a long time. Lamb[7] has obtained the equations governing the free vibration of the solid sphere, while Chree[8] has developed these equations in convenient spherical coordinates rather than Cartesian coordinates. On the other hand, the free oscillation behaviour of multi-layered hollow spheres was studied by Jiang *et al.*[9]. The natural frequency of yeast cells was studied for both spherical and elliptical configurations[10]. However, no significant difference was found between these two shapes of the cell while estimating the natural frequency.

In the present study, both normal and cancerous cells (breast and prostate cancer) are modelled as spheres in order to determine their natural frequencies along with the modes of vibration at these frequencies. The results of the work are likely to serve as a tool for selective killing of cancer cells, sparing the healthy ones based upon their natural frequency.

Both normal and cancer cells are modelled as a sphere. The spherical cell model has a maximum diameter of 30, 40 and 50 μm. In all the three models, the elastic wall of the cell has a thickness of 200 nm. The cells are modelled as a linear elastic material. To compare the natural frequencies of normal and cancer cells, modal analysis is carried out in ANSYS 13.0 for both breast and prostate cells. The boundary conditions for this analysis is a non-zero value and the displacement constraints are confined on the node at top of the modelled cell. The modelled cells are allowed to freely vibrate and the natural frequencies are computed. The element type used for the numerical analysis is a shell. It is a simple but sophisticated four-node shell-63 element for computational simulations of isotropic and elastic shells. Two types of cancer cells were selected, namely prostate and breast cancer cells as they share some similarity since they are hormone-dependent. It is hypothesized that the natural frequency of both these types of cancer cells may provide information about the computed natural frequency of the cancer cells. Properties of the normal and cancer cells were utilized directly from the literature.

To estimate the natural frequency, cell properties of MCF-10A (normal) and MCF-7 (cancerous) were utilized. The elastic modulus of MCF-10A cells was kept constant at 0.73 kPa and the Poisson's ratio was 0.49 (ref. 10). The density was considered as 1020 kg/m^3 (ref. 11). Similarly, for the MCF-7 cells, the elastic modulus was kept constant at 0.425 kPa and the Poisson's ratio was 0.49 (ref. 12). The density of the MCF-7 cell was considered as 994 kg/m^3 (ref. 13).

To perform the modal analysis of prostate cells, we chose normal BPH cells as well as cancerous cell line LNCap. The elastic modulus of normal prostate cells (BPH) was kept constant at 2.797 kPa and the Poisson's ratio was 0.49 (ref. 11). The density of the BPH cells was considered as 1151 kg/m^3 (ref. 14). Similarly, for the cancerous prostate LNCap cells, the elastic modulus was kept constant at 1.401 kPa, with the Poisson's ratio of 0.49 (ref. 11). The density of the prostate cancer cells was assumed to be 1018 kg/m^3 (ref. 15).

Statistical analysis of the results was done using graph pad prism. One-way ANOVA was performed to estimate the statistical significance. A probability value of $P < 0.05$ was considered significant.

The natural frequencies of the normal and breast cancer cells of three different dimensions, namely 30, 40 and 50 μm were computed. Natural frequencies of normal breast cells (MCF-10A) at these three dimensions showed

Table 1. Mean natural frequencies for normal and breast cancer cells

No. of modes (Hz)	$n = 1$*	$n = 2$*	$n = 3$*	$n = 4$*	$n = 5$*
Natural frequency of normal breast cells	6.2579 ± 2.2	14.516 ± 1.18	17.071 ± 1.29	261.40 ± 2.8	1288.5 ± 2.37
Natural frequency of cancerous breast cells	4.8369 ± 1.9	11.212 ± 1.13	13.195 ± 1.34	202.4 ± 3.18	995.96 ± 2.78

*Mean differences are significant for normal and breast cancer cells ($P < 0.05$).

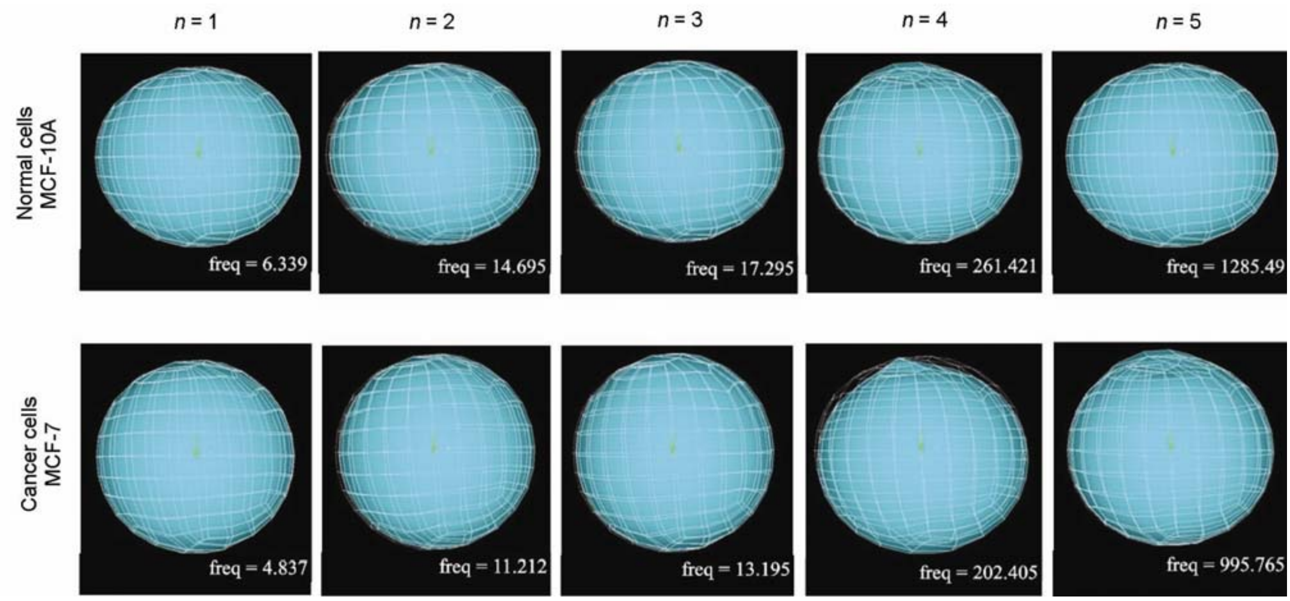

Figure 1. Modes of vibration of normal and cancerous breast cells with 40 μm diameter. Normal (MCF-10A) and breast cancer cells (MCF-7) were modelled using ANSYS software and results of modal analysis depicting various modes of vibration at each natural frequency are given.

no significant difference ($P > 0.05$) between them. Similarly, for breast cancer cells (MCF-7), the difference in the natural frequencies for the three dimensions was insignificant. However, while comparing the normal with breast cancer cells, the natural frequency of normal cells (MCF-10A) was always higher than that of the MCF-7 cancerous cells ($P < 0.05$). Table 1 shows the mean natural frequencies of normal and breast cancer cells. Figure 1 shows the modes of vibration of the cells with 40 μm diameter at their respective frequencies for both cell lines. It is evident that their modes of vibration are different at each natural frequency computed.

The natural frequencies of the normal and prostate cancer cells of three different dimensions, namely 30, 40 and 50 μm were computed. Natural frequencies of normal prostate cells (BPH) at these three dimensions showed no significant difference ($P > 0.05$) between them. Similarly, for breast cancer cells (MCF-7), the differences in the natural frequencies for the three dimensions were insignificant. However, while comparing the normal with prostate cancer cells, the natural frequency of normal cells (BPH) was always higher than that of LNCap cancerous cell ($P < 0.05$). Table 2 shows the mean natural frequencies of normal and prostate cancer cells. Figure 2 shows the modes of the vibration of the cells with 40 μm diameter at their respective frequencies for both cell lines. Their modes of vibration are different at each natural frequency computed.

Cancer is the second common cause of death worldwide[1]. The cure for cancer has always been associated with side effects in the patients undergoing chemotherapy. Hence, there is a constant demand for new modes of treatment, free from unwanted side effects. In this scenario, to increase the effectiveness of destroying the cancer cells without side effects, we propose an unconventional method for treating cancer by utilizing the cell properties like elasticity and natural frequency.

Civil engineers estimate the natural frequencies of structures such as dams, bridges, etc. before building them, in order to prevent them from collapsing as the result of resonance due to natural vibrations, when they meet equivalent load with the same natural frequency of the structures. Likewise estimation of natural frequencies of different prosthesis has been considered in order to avoid rupture when implanted[16]. The natural frequencies are different for the cells in different biological conditions. Thus, by exploiting the natural frequency of the cell as a tool for cancer treatment, we may be able to reduce the burden associated with chemotherapy, as it specifically targets the cancer cells while sparing the

Table 2. Mean natural frequencies for normal and prostate cancer cells

No. of modes (Hz)	$n = 1$*	$n = 2$*	$n = 3$*	$n = 4$*	$n = 5$*
Natural frequency of normal prostate cells	11.553 ± 2.1	26.865 ± 1.5	31.612 ± 2.1	482.15 ± 3.45	2369.9 ± 1.86
Natural frequency of cancerous prostate cells	8.6941 ± 1.9	20.218 ± 1.2	23.790 ± 2.38	362.85 ± 2.97	1783.5 ± 2.23

*Mean differences are significant for normal and prostate cancer cells ($P < 0.05$).

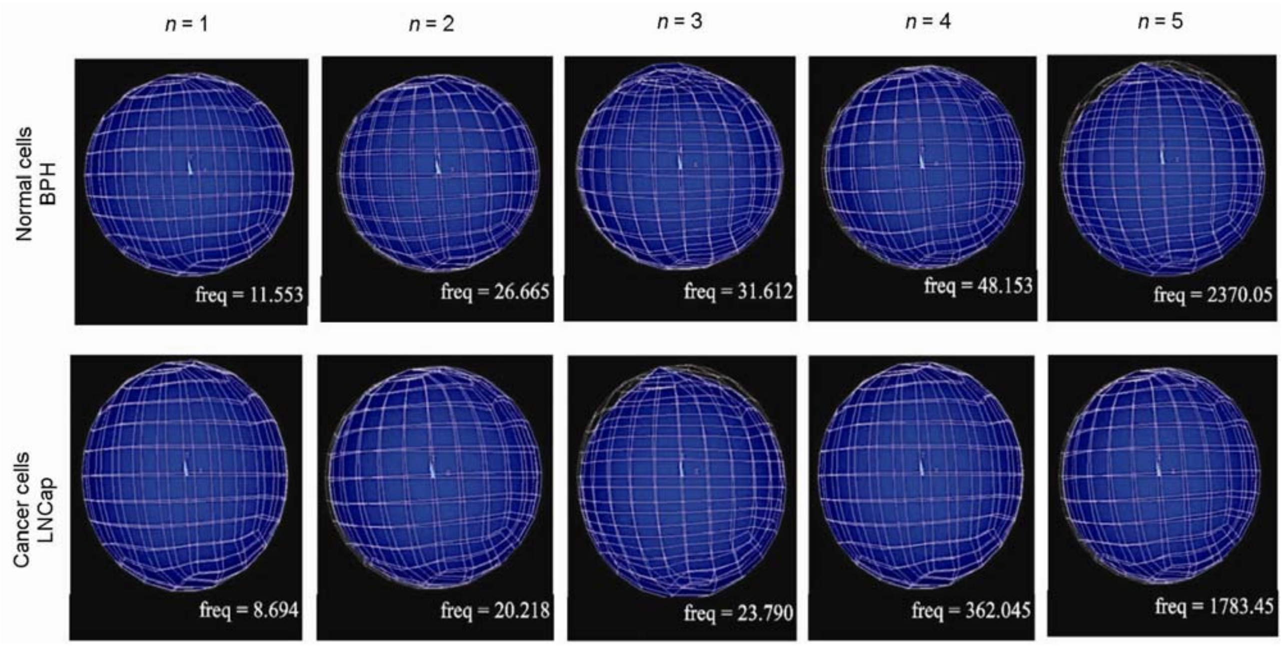

Figure 2. Modes of vibration of normal and cancerous prostate cells with 40 μm diameter. Normal (BPH) and prostate cancer cells (LNCap) were modelled using ANSYS software and results of modal analysis depicting various modes of vibration at each natural frequency are given.

healthier ones. From this point of view, in the present study, we determine the natural frequencies and mode shapes of cancer and normal cells.

The results obtained show that the natural frequencies of breast and prostate cancer cells are lower than those of the respective normal cells. The obtained results are analogous to the recent observations related to the estimation of natural frequency for normal and cancer cells[17]. The results also show that the natural frequency of cancer cell cytoskeleton is lower than that of normal cells. Tables 1 and 2 show the relation between mechanical properties and natural frequency. The human body is made up of different kinds of cells, which are adapted to execute specific functions of their own. The cells vary both in appearance and functions performed, implying that their mechanical properties will also differ. Similarly, in our study, the normal breast and prostate cells have different mechanical properties. It is commonly known that the natural frequencies of structures are influenced by their mechanical properties[16]. This is well reflected in their computed natural frequencies.

Both the cancer and normal cells are modelled as a sphere without nucleus. This is because it was recently shown that functional elements present in the nucleus have little influence over the natural frequencies of the cells. Further, the variations of cell size do not yield any significant variations in the natural frequency of cells. The results of our study corroborate these observations. It has also been shown that the shape of the cells, whether spherical or ellipsoidal, does not significantly influence the natural frequency of yeast cells[10,18].

Since the frequency of normal and cancer cells is different, it is evident that mechanical properties of the cells such as their size, wall stiffness and elasticity are the best signatures of cell status. The absolute measurement of these properties of biological systems is complex, and the simple comparison of two different oscillation frequencies would yield a better idea about the changes in the biological system[19]. Hence, modal analysis provides an idea about the particular frequency we could assign to the pool of normal and cancer cells. Only cancer cells will resonate and vibrate intensively leading to their selective destruction while sparing the normal cells. This can be related to a recent study which demonstrates that the MCF-7 cells can be selectively killed under culture conditions using low-intensity ultrasonic irradiation at *in silico*-determined resonance frequencies[20].

However, there are some limitations in the present study. We are estimating the natural frequency of a single cell, whereas in the human body cells are closely packed in tissues and will have a different set of normal frequencies; but the frequencies are likely to be different between normal and cancerous cells. Besides this, a study on the combinational treatment of chemotherapy and irradiation at natural frequency may be useful.

Modal analysis indicates that the natural frequency obtained for normal cells is always higher than that of the cancer cells (both breast and prostate cancer cells) at each of the corresponding modes. Variation in cell dimension does not significantly alter the natural frequency of the cells. Modes of vibration of the cancer and normal cells show variation between them. Furthermore, the natural frequency increases with increasing Young's modulus and density of the cells. In conclusion, the study shows that by exploiting the natural frequency of the cancer cells as a tool for treatment, the burden associated with chemotherapy and drug resistance may be overcome by specifically targeting the cancer cells.

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Integrated role of SST, PAR and CDOM in summer reef bleaching during 2010 and 2011 along the Lakshadweep Islands

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The role of sea-surface temperature (SST), photosynthetically active radiation (PAR) and chromophoric dissolved organic matter (CDOM) on bleaching events along the Lakshadweep archipelago was studied for the summer of 2010 and 2011. The present study revealed similar SST pattern (30.8–31.9°C) and high PAR availability (48–50 E m^{-2} day^{-1}) during the summer weeks of 2010 and 2011. However, the CDOM content varied significantly between 0.5 and 7 during

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