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# Investigation of the influence of viscoelasticity on oncotripsy

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## Highlights

- Oncotripsy remains viable when viscoelasticity is taken into account.
- The main effect of viscoelasticity is a modest reduction in the resonant natural frequencies of cells.
- Based on viscoelastic effects, the time to lysis of cancerous cells during harmonic excitation is increased.

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## Abstract

Oncotripsy has recently been proposed as a means of selectively targeting cancer cells via resonant harmonic excitation (Heyden and Ortiz, 2016). The method makes use of aberrations in material properties of cancerous cells which allow to induce local resonance up to membrane lysis in cancerous cells while leaving healthy cells intact. Here, we explore the influence of viscoelasticity on the oncotripsy effect. Based on Rayleigh damping, we derive viscoelastic target frequencies and simulate the fully nonlinear transient response of healthy and cancerous cells at resonance. Results confirm the viability of oncotripsy with viscoelastic material behavior of cell constituents accounted for.

*Keywords:* Oncotripsy; Viscoelasticity; Local resonance; Cell lysis

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## 1. Introduction

The method of oncotripsy, first proposed in [1], exploits aberrations in the material properties and morphology of cancerous cells in order to target them selectively by means of ultrasound radiation. Experimental investigations have shown that the size difference between normal nuclei, with an average diameter of 7–9 microns, and malignant nuclei, which can reach a diameter of over 50 microns, constitutes an important criterion for malignancy [2]. In addition, the material response of live metastatic cancer cells has been found to be more than 80% softer than that of healthy cells [3], and cancer cells with the highest invasion and migratory potential have been found to be up to five times softer than healthy cells [4]. Conversely, experimental investigations on hepatocellular carcinoma cells (HCC) have revealed that an increase in stiffness of the extracellular matrix (ECM) promotes HCC cell proliferation [5] and advances malignant growth [6]. Since the stiffness of the nucleolus is higher than that of other nuclear domains [7–9]

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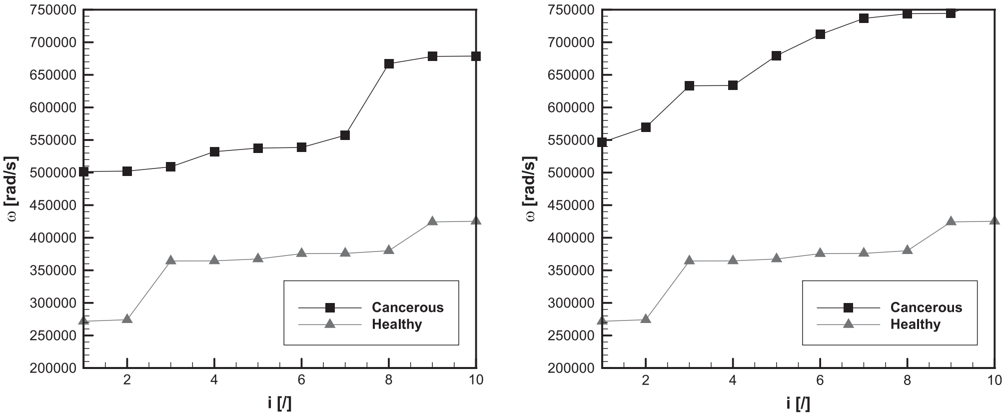

Fig. 1. Eigenfrequencies calculated from the standard symmetric linear eigenvalue problem [1]. Left: Comparison of the lowest ten eigenfrequencies between healthy and cancerous cells based on changes in material properties. Right: Comparison of the lowest ten eigenfrequencies between healthy and cancerous cells based on changes in material properties with a simultaneous nuclear/nucleolar volume increase by 100%.

with a simultaneous increase in mass density [10], nuclei and nucleoli act as local resonators within cells that are subjected to harmonic excitation. Owing to the aforementioned aberrations in material properties and morphology, the eigenfrequencies at which local resonance occurs are expected to differ between healthy and cancerous cells.

Numerous experimental studies have additionally suggested that the material behavior of the different cell constituents is viscoelastic. Based on particle-tracking microrheology, Panorchan et al. [11] determined viscoelastic properties of the cytoplasm of human umbilical vein endothelial cells. Using micropipette aspiration techniques, Guilak [12] quantified the viscoelastic properties of isolated nuclei of articular chondrocytes and found that nuclei are characterized by a viscoelastic material behavior which is almost twice as viscous as the material behavior of the cytoplasm. In an investigation involving both cancerous and healthy cells, Zhang et al. [13] showed that HCC cells exhibit approximately the same viscoelastic properties compared to normal hepatocytes. Measurements of individual cytoskeletal biopolymers have furthermore been presented in [14], where the stress versus strain response and storage modulus $G'$ have been recorded for three major cytoskeletal fibers.

In a recent numerical study [1], we have shown that cancerous eigenfrequencies lie above those of healthy cells, with a typical gap in the lowest natural frequency of about 229,812 rad/s, cf. Fig. 1. We also show that the resonant growth rates of cancerous eigenfrequencies can exceed those of healthy cells, an important requirement for selectively targeting cancerous tissues while leaving healthy cells (potentially possessing close neighboring eigenfrequencies) intact. In [1], the main determining factor responsible for the observed higher eigenfrequencies of cancerous tissues is furthermore determined to be the extracellular matrix (ECM), due to its increased stiffness. Fig. 2 illustrates that the eigenfrequencies of a cancerous/cancerous ECM/cell system lie above those of the healthy case, while the eigenfrequencies of the healthy/cancerous ECM/cell system are decreased.

However, the calculations presented in [1] assume elasticity and neglect viscoelastic effects. In the present study, we investigate the influence of viscoelasticity on the oncotripsy effect. We start by outlining the material parameters and geometrical model components used in the presented numerical study, followed by a derivation of viscoelastic target frequencies and simulations of the fully nonlinear viscoelastic transient solution at resonance.

## 2. Cell geometry and material parameters

In mammalian cells, the nucleus, as the largest cellular organelle, occupies about 10% of the total cell volume [15,16]. It is surrounded by the cytosol, a viscous solid containing several subcellular structures such as the golgi apparatus, the mitochondrion, and the endoplasmic reticulum as illustrated in Fig. 3. The cytosol and other organelles contained within the plasma membrane, for instance mitochondria and plastids, form the so-called cytoplasm. The nucleus is bounded by the nuclear envelope and contains the nucleoplasm, a viscous solid similar in composition to the cytosol. It furthermore comprises the nucleolus, which constitutes the largest structure within the nucleus and consists of proteins and RNA.

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