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Short communication

Effects of diurnal loading on the transport of charged antibiotics into intervertebral discs

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ABSTRACT

The objective of this study was to quantitatively analyze the effect of diurnal loading on the transport of various charged antibiotics into negatively charged human intervertebral disc (IVD). Transport of charged antibiotics into a human lumbar disc was analyzed using a 3D finite element model. The valence (z) of the electrical charge of antibiotics varied from z = +2 (positively charged) to z = −2 (negatively charged). An uncharged antibiotic (z = 0) was used as a control. Cases with transient antibiotic concentration at disc boundaries [to mimic intravenous (IV) infusion] were simulated. Our results showed that diurnal compression increased the concentrations in the nucleus pulposus (NP) region, but degreased the concentrations in the annulus fibrosus (AF) region for all charged or non-charged drugs. The overall concentration (averaged over disc) increased with diurnal compression. The diurnal compression had more effects on negatively charged antibiotics than positively charged ones. For example, at day 5 with diurnal compression, the diurnal compression increased the concentration of negatively charged drug (z = −1) in NP by 18.3%, but only by 6.6% for positively charged one (z = +1). In AF, diurnal compression decreased the concentration by 13.2% for negatively charged drug (z = −1) versus 1.2% for positively charged one (z = +1). Note these percentages are the averaged values over day 5. This study provides quantitative information on understanding the mechanisms of charged drug transport in human IVDs.

1. Introduction

Intervertebral disc (IVD) infection is caused by the bacteria invasion into the disc space. The incidence of disc infection is growing due to many factors such as the aging population, the rise of intravenous (IV) drug abuse, an increase in spinal surgeries, particularly in immunosuppressed patients (e.g., HIV, cancer, rheumatic disease patients) (Acosta et al., 2006). Currently, treatment of disc infections is difficult and costly, often requiring weeks of inpatient care and IV administered antibiotics.

Many commonly used antibiotics are small molecules, and electrically charged. Due to the avascular nature of the IVD tissue, transport of antibiotics into the disc is mainly through diffusion from vasculatures surrounding the disc. The rate of antibiotics transport into the IVD depends on several factors, including antibiotic molecular size, electric charge (positive or negative), as well as disc tissue properties such as porosity (Currier et al., 1994; Eismont et al., 1987; Gibson et al., 1987; Gu et al., 2003, 2004; Maroudas, 1976; Riley et al., 1994; Thomas et al., 1995; Urban et al., 1977; Zhu et al., 2016). In general, drugs with smaller size, and/or with positive charge have easier access to, or higher uptake in the discs than the ones with larger sizes and/or negative charge (Currier et al., 1994; Eismont et al., 1987; Gibson et al., 1987; Riley et al., 1994; Thomas Rde et al., 1995; Urban et al., 1977; Zhu et al., 2016) because IVDs are negatively charged due to the charged groups (e.g., SO_3^-, COO^-) on the side chains of proteoglycan, one of the major component of the IVD matrix (Urban and Maroudas, 1979). The concentration of charged groups is called fixed charge density.

Solute transport in the disc is also affected by mechanical loading (Arun et al., 2009; Ferguson et al., 2004; Gullbrand et al., 2015; Huang and Gu, 2008; Jackson et al., 2011; Urban et al., 1982; Yao and Gu, 2004, 2006). It is generally found that static loading decreased the transport rate of solutes in human IVDs (Arun et al., 2009; Huang and Gu, 2008; Jackson et al., 2011), while dynamic loading enhanced the transport rates of solutes (Ferguson et al., 2004; Gullbrand et al., 2015; Huang and Gu, 2007; Urban et al., 1982; Yao and Gu, 2006). However, most of the studies are focused on non-charged solutes, and to our knowledge, there is limited information on how mechanical

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loading affects the transport of charged solutes in the highly negatively charged human disc. Due to the charged nature of the IVD and some antibiotics, electric interaction between charged tissue and antibiotics plays an important role in governing antibiotic penetration rate, antibiotic concentration profile, and duration for antibiotic maintaining its concentration at the level above minimal inhibitory concentration within the IVD.

Thus, the objective of this study was to quantitatively analyze the effect of dynamic loading (e.g., diurnal loading) on the transport of charged antibiotics into charged IVDs using a finite element method. Such knowledge is important for treating disc infections with the proper dosage and timing of antibiotics.

2. Methods

A previously developed finite element model (Zhu et al., 2016) was used in this study, in which the transport of various charged antibiotics into human lumbar discs without mechanical loading was analyzed. In the current study, the method was similar to previously published paper (Zhu et al., 2016), except the mechanical loading condition. In the current study, mechanical compression with the profile shown in Fig. 1c was applied on the top of the vertebra to mimic the diurnal loading on the IVD. This compression profile (Fig. 1c) was determined based on experimental data that the disc height decreased by a maximum of 1.3 mm at the end of the 16.5-h day activity, and it recovered back to its original thickness at the end of the 7.5-h sleep (Broberg, 1993), assuming the disc has a height of 10 mm. The material properties (including the mechanical properties, transport properties, and electrochemical properties) used in this study can be found in Table 1 of our previous study (Zhu et al., 2016). In real situation, there is no discontinuity in permeability or diffusivity at the annulus fibrosus-nucleus pulposus (AF-NP) boundary or interface. However, information on these properties at AF-NP boundary is not available in the literature. In order to avoid possible discontinuity in transport properties at the AF-NP interface, in the current study, the constitutive relationship for hydraulic permeability and diffusivities for NP were used for those for AF.

Three groups of antibiotics were investigated: a positively charged group, a negatively charged group, and a neutral group. To eliminate the effects of differences in molecular characteristics on the transport of antibiotics into discs, all the antibiotics were assumed to have the same molecular properties [e.g., molecular weight (400 g/mol), diffusivity in water at 37 °C (6.2×10^{-10} m^2/s), and hydraulic radius (0.53 nm)], except electrical charge. The reason for choosing this molecule weight of 400 g/mol in our simulation is that many commonly used antibiotics have a similar molecular weight (around 300–500 g/mole).

After the disc reaches steady state upon the application of this diurnal compression, a transient concentration was applied at the disc boundary with a function of $c = \frac{0.401}{t_0} t\ (if\ t <= t_0) + (0.197e^{-7.762\times10^{-4}(t-t_0)} + 0.204e^{-8.39\times10^{-5}(t-t_0)})\ (if\ t > t_0)$ (mM, where t_0 = 30 s), see Fig. 1d, to mimic drug level changes in the serum post intravenous (IV) administration as reported in the literature (Currier et al., 1994; Pinto et al., 2011; Shi et al., 2010; Walters et al., 2006). This boundary condition was repeated every 24 h to simulate multiple IV infusions. For the convenience (without losing generosity), we assumed that the blood-disc partition coefficient is unity at both the cartilaginous endplate (CEP) boundary and the AF periphery for the antibiotics in the simulation. The uptake of the antibiotics by the cells was not considered in the current study due to lack of information in the literature. Transport of charged antibiotics in IVD under diurnal compression (Fig. 1c) was studied and compared to those without compression.

3. Results

Diurnal compression increased the concentrations in the NP region for all charged or non-charged drugs, but generally decreased the concentrations in the AF region (Figs. 2 and 3). The overall concentration (averaged over disc) was increased with

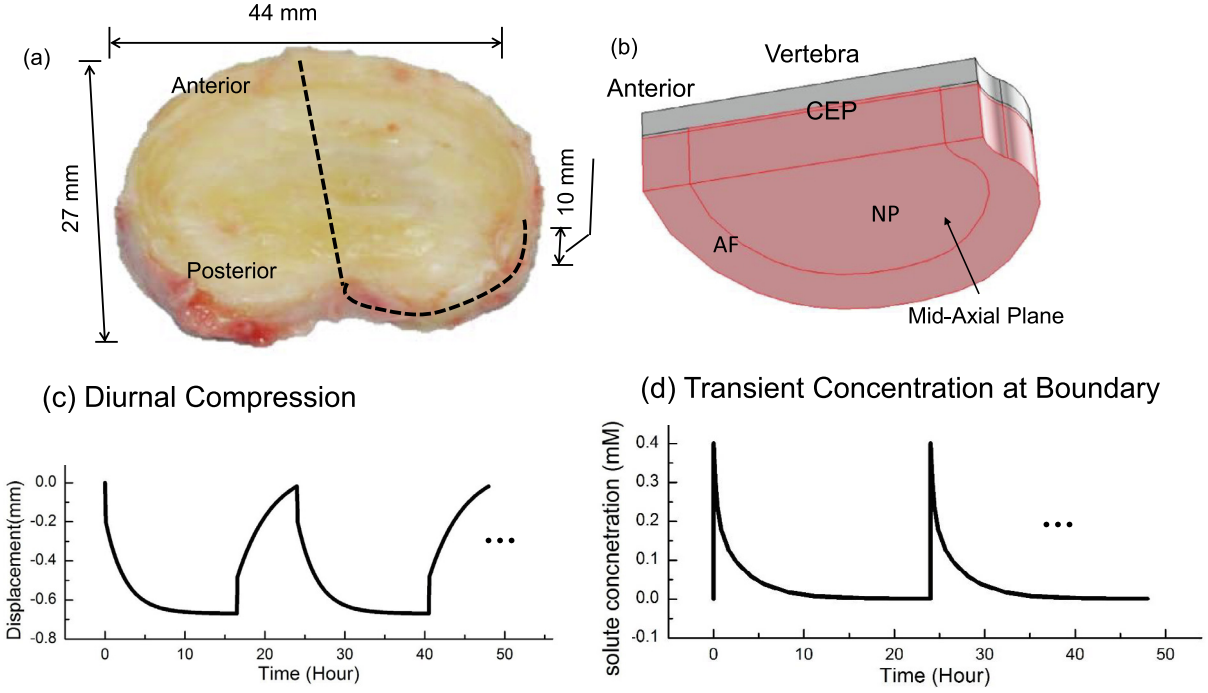

Fig. 1. (a) Picture of a human lumbar intervertebral disc (IVD, L2-3, non-degenerated). (b) Schematic of a quarter of the IVD-vertebra segment used in the FEM analysis (due to symmetry). (c) Schematic of the diurnal compression (on a quarter of the disc). (d) Schematic of the transient antibiotic concentration at the disc boundary. NP: Nucleus pulposus. AF: Annulus fibrosus. CEP: Cartilaginous endplate.

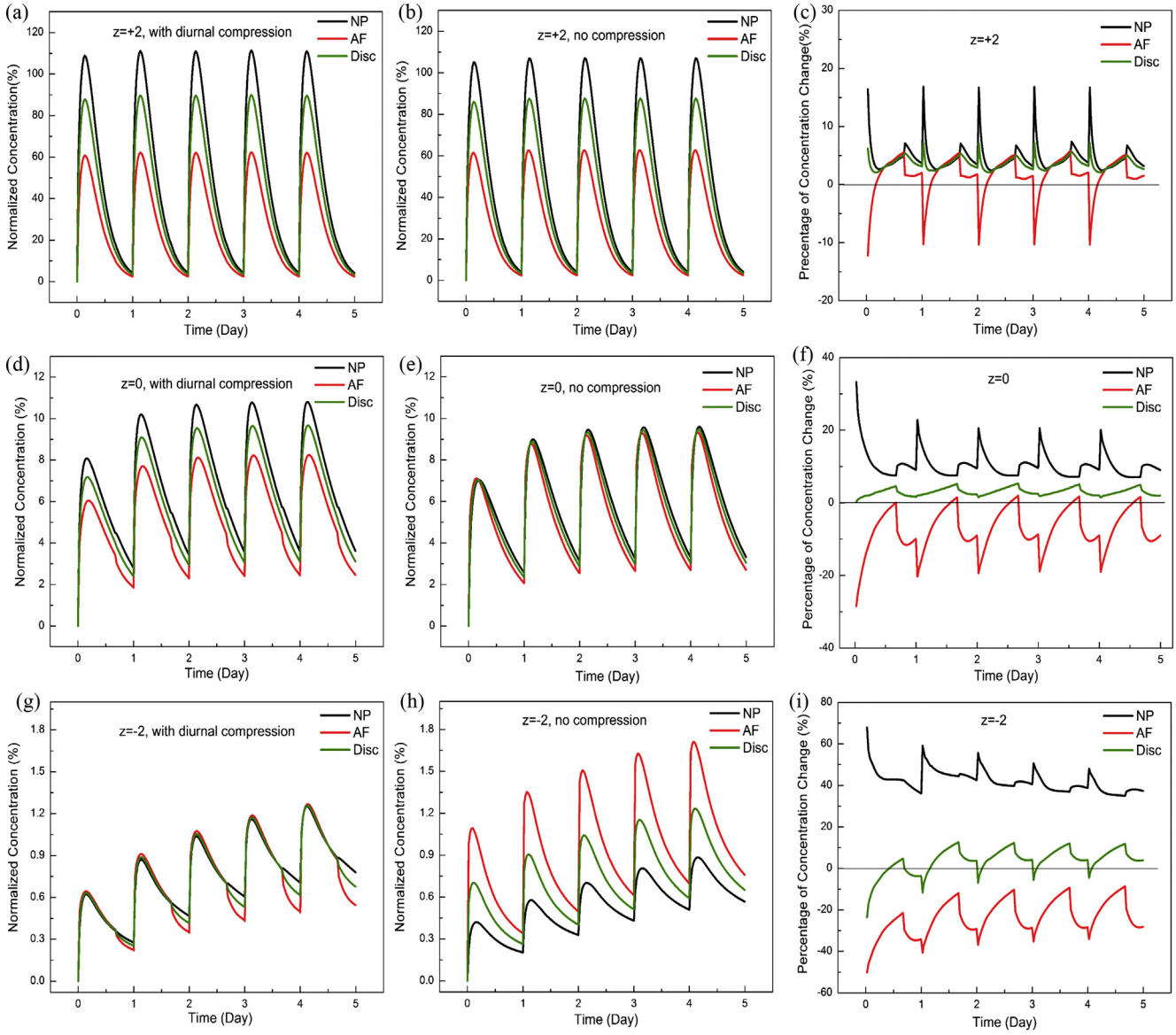

Fig. 2. Normalized antibiotic concentrations in the disc, with diurnal compression (a, d, g), without diurnal compression (b, e, h), and their relative changes due to diurnal compression (c, f, i). In (a, c, d, f, g, i), the concentrations were normalized to the peak value of the concentration in serum (i.e., 0.4 mM)], while in (c, f, i), relative changes in concentrations (due to diurnal compression) to those without diurnal compression. z = valence of the antibiotic. NP: Nucleus Pulposus; AF: Annulus Fibrosus.

diurnal compression (Fig. 2). The diurnal compression had more effects on negatively charged antibiotics than positively charged ones (Fig. 3). For example, at day 5 with diurnal compression, the diurnal compression increased the concentration of negatively drug ($z = -1$) in NP by 18.3%, but only by 6.6% for positively charged one ($z = +1$). In AF, diurnal compression decreased the concentration by 13.2% for negatively charged drug ($z = -1$) versus 1.2% for positively charged one ($z = +1$), see Fig. 3c. Note these percentages in this example are averaged values over the day 5. The effect of diurnal compression on the concentration in the disc monotonically and nonlinearly decreased when the charge number (or valence) increased from −2 (negatively charged) to +2 (positively charged), see Fig. 3c.

4. Discussion

The objective of this study was to investigate the effect of diurnal loading on antibiotic penetration into IVD with IV infusions. Due to transient drug concentration at the disc boundary (Fig. 1d), the concentration gradient in the disc varies with time. During the penetration process, IVD also deforms under diurnal loading (Fig. 1c), causing changes in tissue hydration and its related transport properties (Gu et al., 2003, 2004; Johnson and Deen, 1996; Mackie and Meares, 1955; Masaro and Zhu, 1999; Mow et al., 1980). The strain field in the IVD is complex, mainly due to its 3D geometry (Fig. 1a). The combination of concentration gradient and mechanical effects governs the transport of non-charged drug (i.e., $z = 0$) in the IVD. In some regions at a certain time, the concentration gradient and mechanical effects might work together to enhance the transport of non-charged antibiotic; or they might work against each other to impede its transport, resulting in a higher (or lower) antibiotic concentration in some regions relative to those without mechanical compression. This might explain why dynamic compression enhances the concentration of non-charged antibiotic in the NP, but not in the AF (Figs. 2 and 3).

For charged drugs, the driving force is the gradient of its electrochemical potential which is explicitly related to the valence of the drug (Gu et al., 1998; Lai et al., 1991). The electric interaction of charged drug with charged tissue further enhances the effect of dynamic compression on drug transport. Since the concentration

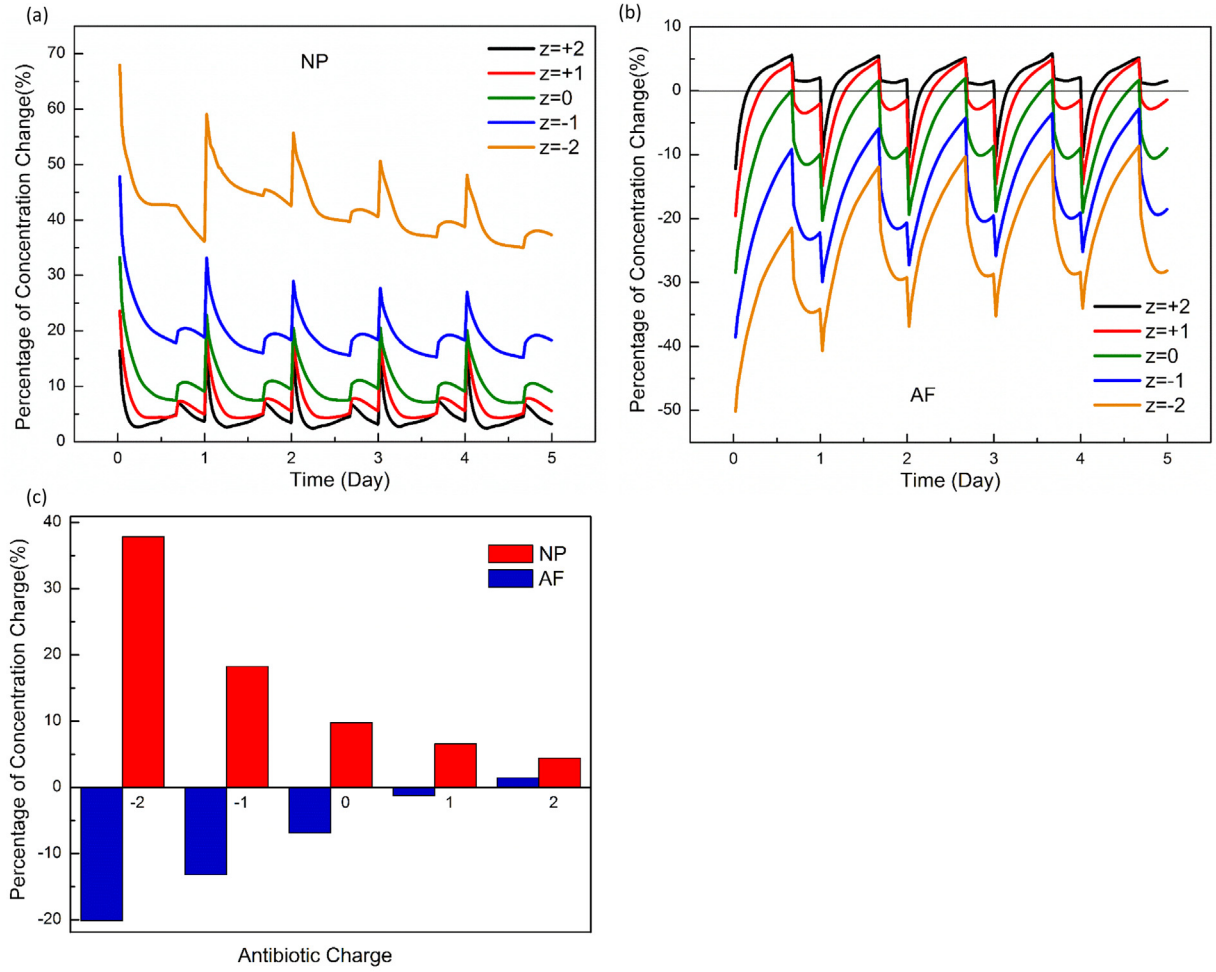

Fig. 3. Comparisons of the relative change in concentration due to diurnal compression for various electrically charged antibiotics in NP (a) and AF (b). (c) Correlation between antibiotic charge and percentage of concentration change (averaged over day 5). NP: Nucleus Pulposus. AF: Annulus Fibrosus.

is lower in IVD with higher negatively charged drugs (even with dynamic compression), compared to that of positively charged ones, the effect of dynamic compression on the change in relative concentration is more pronounced for higher negatively charged drugs (Fig. 3).

With transient antibiotic concentration at tissue boundaries, our simulation predicts that diurnal compression is beneficial for enhancing transport of charged and non-charged antibiotics into the NP region of the disc (Figs. 2 and 3). Our result is consistent with an in-vivo study on the transport of gadodiamide (small neutral molecule, M_w = 573 g/mol) into the NP of rabbits with the IV injection (Gullbrand et al., 2015). In this in-vivo study, the authors found that the transport was enhanced in the NP of rabbits under dynamic compression. In our study, our model predicted that the concentration of non-charged antibiotic in the NP increased with diurnal compression.

In order to understand drug transport in the disc with higher loading frequency, we also simulated the cases with 2 and 4 cycles of compression per day. The compression profile was in a half-sinusoidal fashion with the peak strain of −13%. Our results show that dynamic loading with higher frequency enhances the concentration of both charged and non-charged antibiotics in the NP, and decreases the concentrations in the AF region (Fig. 4), which is consistent with our findings with diurnal loading.

Some limitations in the current study include that the anisotropy of the transport properties in AF was not considered in this study, this may affect the concentration distribution of the antibiotic in the AF. However in this study, we used the average concentration in the AF region in our analysis, thus the findings related to AF in our current study may not be significantly influenced by this limitation. Another limitation is that the repeated IV infusions have the same frequency as the diurnal loading in this study. In the future studies, we will investigate cases with different infusion frequencies, to further understand the interaction between mechanical and chemical loading.

In conclusion, in this study, we numerically investigated the effect of diurnal loading on transport of charged antibiotics in the negatively charged human IVDs under transient antibiotic concentration at disc boundary. Our results indicate that diurnal compression enhances (reduces) drug concentration in NP (in AF), but overall concentration in disc increases with diurnal loading. Our predicted results are consistent with the findings reported in the literature. This study provides a new insight into the mechanism of transport of charged antibiotics into the disc under dynamic loading conditions.

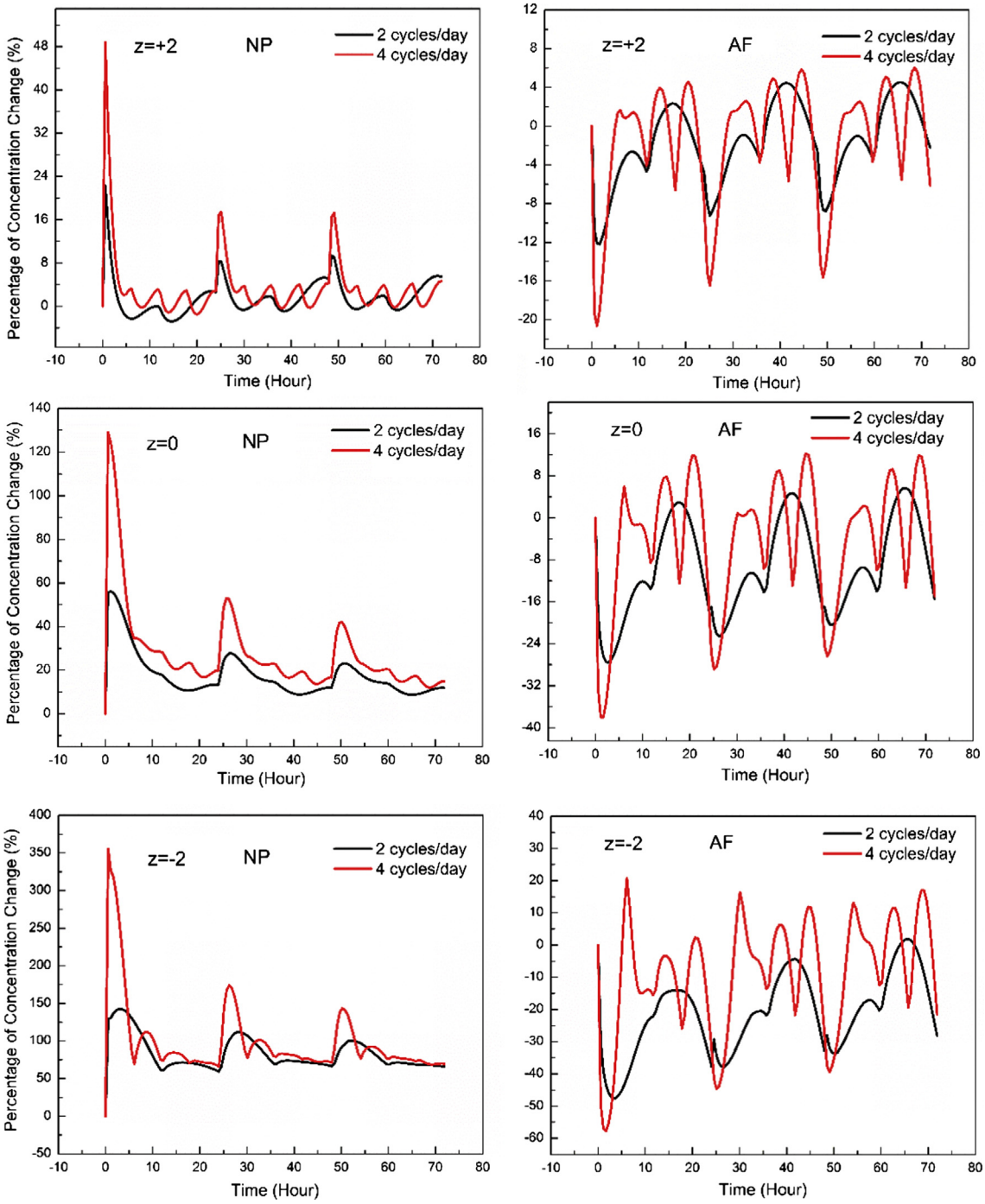

Fig. 4. The effect of loading frequency on percentage change in drug concentration (relative to those without dynamic compression). NP: Nucleus Pulposus. AF: Annulus Fibrosus.

Conflict of interest statement

No financial support or benefit has been obtained from any commercial source related directly or indirectly to the scientific work reported in this manuscript.

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