Comparison of the Effects of Possible Mechanical Stimuli on the Rate of Biochemical Reactions

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The aim of this work is to address the question of what constitutes a mechanical stimulation of biochemical reactions in general and further to compare the importance of the two possible mechanical stimulations: shear rate and the rate of volume variation. Using linear nonequilibrium thermodynamics, the Curie principle (the relation for coupling phenomena) is retrieved for a phenomenological relation for a scalar flux in an isotropic system. From these phenomenological relations for the rate of chemical reaction, it is established that the only scalar quantity related to the rate of deformation tensor $\boldsymbol{D}$ that cannot be neglected is the rate of volume variation $D^{(1)}$. This leads us to the conclusion that, although tissues are exposed to all variety of mechanical factors: straining, shear, pressure, and even dynamic electric fields, the volume variation rate $D^{(1)}$ is the most important mechanical stimulus driving the processes in them.

Introduction

Tissue engineering is believed to be a promising technique for tissue replacement. Coletti et al. proposed an interesting mathematical model for tissue engineering in bioreactors including convection, diffusion, or geometric properties of scaffolds,[1] whereas Costa-Pinto et al. studied the growth of bone tissue on two scaffolds by demonstrating the presence of a mineralized extracellular matrix together with osteogenic gene markers.[2] However, both approaches neglected mechanical stimuli, which are actually recognized as an important factor in ex vivo tissue cultivation, as they promote tissue formation[3,4] and even modulate the phenotype of involved cells.[5]

In some bone remodelling processes, mechanical stimulation may be neglected, as possibly in growth of calcium phosphate from physiological solution.[6] Nevertheless, in the case of the majority of biochemical processes in bone tissue, the significance of mechanical stimulation is widely accepted. Heřt described an interaction between the mechanical stimulation of local cells and the bone adaptation process in the 1970s,[7] while Frost observed the same behavior in his clinical praxis and summed it up in his "Utah paradigm".[8,9] More recently, the fundamental importance of dynamic loading has been accepted. A comparison of static versus dynamic loading effects on bone remodelling is given in an inspectional review by Ehrlich and Lanyon.[10] Furthermore, Robling provides experimental results that confirm the essential importance of dynamic loading.[11] It is worth mentioning that Heřt referred to this phenomenon in his observations more than 35 years ago.[7]

Despite great advancements in the knowledge of mechanosensing and mechanotransduction, it is still not clear what type of mechanical stimulation is the most suitable (osteogenic) for bone. The aim of this work is to address the above-mentioned question about the proper mechanical stimulation of biochemical reactions in general and to compare the importance of the two possible mechanical stimulations: shear rate and rate of volume variation. Nonequilibrium thermodynamics will be used for this comparison, as it is a highly appropriate and useful tool for dealing with multidisciplinary problems or for finding relations among coupled phenomena. For example, Demirel and Sandler provide a review of the field of nonequilibrium thermodynamics, showing its importance in a large variety of biological, chemical, and mechanical applications. For instance, developments in coupled transport and rate processes suggest that nonequilibrium thermodynamics can be quite useful.[12] Fort et al. proposed a model for nonequilibrium chemical reacting systems based on an assumption that the specific entropy of the system is a function of the net reaction rates, as well as classical variables.[13] Jou et al. presented many examples of thermodynamics applications, although these problems are nowadays better apprehended thanks to extended irreversible thermodynamics.[14] Nicolis and Daems studied the meaning of entropy in dynamical systems with noise using irreversible thermodynamics.[15] Qian introduced nonequilibrium statistical thermodynamics that enable the researcher to describe a wide range of phenomena such as molecular motors, nonlinear chemical oscillation, and single-molecule enzyme kinetics.[16] Rubí et al. dealt with the problem of the applicability of nonequilibrium thermodynamics on overly small systems thermodynamically in a traditional sense. They discussed the validity of essential nonequilibrium thermodynamics equations and demonstrated how to modify and apply thermodynamics formalism at the single-molecule level.[17] For studying bone remodelling, the essential coupling is between chemical and mechanical processes. Oplatka found the equation of state for tetanic contraction in skeletal muscle that relates ATP turnover rate to the external load.[18] In addition, Klika and Maršík showed how mechanical processes may influence rates of chemical reactions by using classical irreversible thermodynamics.[19]

Methods

Using linear nonequilibrium thermodynamics, the Curie principle (coupling) will be retrieved for a phenomenological

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relation for a scalar flux in an isotropic system. Following this, it will be noticeable that the rate of volume variation is the most important mechanical stimulation for biochemical reactions.

To find which processes actually couple, we shall recall an important quantity production of entropy:

$$\sigma(S) = \mathbf{j}_q \nabla \frac{1}{T} - \sum_{i=1}^{r} \mathbf{j}_{\mathrm{D}i}\left(\nabla \frac{\mu_i}{T} - \frac{\mathbf{F}_i}{T}\right) + \frac{1}{T}\boldsymbol{t}_{\mathrm{dis}}:\nabla \boldsymbol{v} + \frac{1}{T}\sum_{\alpha=1}^{s} r_\alpha \mathscr{A}_\alpha \geq 0 \quad (1)$$

The Curie principle explains what kind of cross-effects may be encountered.

From our previous work,[19,20] it is known that the rate of deformation tensor, $\boldsymbol{D}$, is essential in describing the influence of mechanical loading on reaction kinetics. The rate of deformation tensor, which is a second-order tensor, is a time derivative of a Lagrangian finite strain tensor, $\boldsymbol{E}$

$$\boldsymbol{D}^{ij} = \dot{\boldsymbol{E}}^{ij} = \frac{1}{2}\left(\frac{\partial \dot{u}^i}{\partial x^j} + \frac{\partial \dot{u}^j}{\partial x^i}\right) = \frac{1}{2}\left(\frac{\partial v^i}{\partial x^j} + \frac{\partial v^j}{\partial x^i}\right) = \frac{1}{2}((\nabla v)^{ij} + (\nabla v)^{ji}) \quad (2)$$

where small deformations are considered. From here, one can easily follow how the mechanical term in entropy production, $\nabla \boldsymbol{v}$, relates to the rate of deformation tensor, $\boldsymbol{D}$, which does not appear explicitly in entropy production.

Biochemical processes running in a human body can be considered isothermal. The aim of the presented work is to compare the effects of mechanical stimulation on chemical reactions, which means that we are interested in the cross-effect, also called coupling, between mechanical, $(1/\boldsymbol{T})\boldsymbol{t}_{\mathrm{dis}}:\nabla \boldsymbol{v}$, and chemical, $1/T\Sigma_{\alpha=1}^{s} r_\alpha \mathscr{A}_\alpha$, dissipative processes. Hence, the diffusion term may be neglected in entropy production 1 and heat conduction, which is insignificant in isothermal processes.

A second-order tensor $\boldsymbol{T}$ may be characterized by its three invariants (or eigenvalues) $E^{(1)}$, $E^{(2)}$, and $E^{(3)}$. The trace of strain tensor $E^{(1)}$ is usually called *dilatation* (the relative variation of volume). This is not precisely correct, as can be seen when the deformation of a cube is considered, but we will use it nonetheless. True volume change is actually the determinant of the strain tensor, which is equal to $E^{(3)}$ in standard notation. Finally, the second invariant of the strain tensor $E^{(2)}$ describes the shear strain of a material element, and is referred to as a *distortion*. Consequently, the physical interpretation of invariants of the rate of deformation tensor $\boldsymbol{D}$ is as follows: $D^{(1)}$, $D^{(2)}$, and $D^{(3)}$ may be called the *rate of volume variation* (rate of dilatation), *shear rate* (distortion rate), and *true rate of volume variation*, respectively. Moreover, if a law of conservation of mass is used, we have the following:

$$D^{(1)} = \dot{E}^{(1)} = \operatorname{div} \boldsymbol{v} = -\frac{1}{\rho}\frac{\mathrm{d}\rho}{\mathrm{d}t}$$

which supports the used denomination of $D^{(1)}$ as the rate of volume variation.

As we will show, even in an isotropic system there might be coupling between the dissipative processes of different tensorial orders. This coupling is based on the splitting of the tensor $\boldsymbol{D}$, which leads to different results for the three eigenvalues. Following on from this, we will arrive at the aforementioned conclusions from the obtained form of phenomenological relations.

The Scalar Quantity Rate of Volume Dilatation $D^{(1)}$. For simplicity of notation, we consider only a single representative of each tensorial order in entropy production. The production of entropy is then of the form (a useful notation from de Groot and Mazur[21] is used)

$$\sigma(S) = J_s X_s + \mathbf{J}_v \cdot \mathbf{X}_v + \mathbf{J}_a^a \cdot \mathbf{X}_a^a + \boldsymbol{J}_t : \boldsymbol{X}_t \quad (3)$$

Without loss of generality, it may be assumed that the tensorial coefficient $\boldsymbol{L}_{st}$ is of the same kind as the thermodynamic force $\boldsymbol{X}_T$; thus, $\boldsymbol{L}_{st}$ is a symmetric tensor with a zero trace. This follows from the fact that the inner product of two arbitrary second-order tensors can be rewritten into the sum of scalar, vectorial and tensorial terms, where the tensorial term is the inner product of two symmetric second-order tensors with a zero trace. In CIT, the general form of phenomenological relations among fluxes and forces is represented by linear equations. Because we are interested in the rate of chemical reactions (a scalar) and how it is affected by other dissipative processes, we focus only on the first phenomenological relation. Thus, we have the following:

$$J_s = L_{ss} X_s + \mathbf{L}_{sv} \cdot \mathbf{X}_v + \mathbf{L}_{sa}^a \cdot \mathbf{X}_a^a + \mathring{\boldsymbol{L}}_{st(s)} : \mathring{\boldsymbol{X}}_{t(s)} \quad (4)$$

The Isotropic System. A second-order tensor that describes a dissipative process can influence scalar processes (thermodynamic fluxes) because every such tensor can be decomposed into scaled unit tensor and a symmetric and an antisymmetric parts both with zero traces.[21]

In our case, tensor $\nabla \boldsymbol{v}$ may be split in the following way:

$$\nabla \boldsymbol{v} = \frac{1}{3}\mathrm{tr}(\nabla \boldsymbol{v})\boldsymbol{U} + \overline{\nabla \boldsymbol{v}} = \frac{1}{3}\mathrm{tr}(\nabla \boldsymbol{v})\boldsymbol{U} + (\nabla \boldsymbol{v})_{(a)} + (\mathring{\nabla}\boldsymbol{v})_{(s)} = \frac{1}{3}\mathrm{tr}(\nabla \boldsymbol{v})\boldsymbol{U} + (\nabla \boldsymbol{v})_{(a)} + \mathring{\boldsymbol{D}} \quad (5)$$

because tensor $\boldsymbol{D}$ is the symmetric part of tensor $\nabla \boldsymbol{v}$, see eq 2.

Let us now consider an isotropic isothermal system where diffusion can be neglected. Therefore, we have for the entropy production:

$$T\sigma(S) = \boldsymbol{t}_{\mathrm{dis}}:\nabla \boldsymbol{v} + \sum_{\alpha=1}^{s} r_\alpha \mathscr{A}_\alpha = \left(\sum_{\alpha=1}^{s} r_\alpha \mathscr{A}_\alpha + \frac{1}{3}\mathrm{tr}(\nabla \boldsymbol{v})\,\mathrm{tr}(\boldsymbol{t}_{\mathrm{dis}})\right) + (\nabla \boldsymbol{v})_{(a)} \cdot (\boldsymbol{t}_{\mathrm{dis}})_{(a)} + \mathring{\boldsymbol{D}} : (\boldsymbol{t}_{\mathrm{dis}})_{(s)} \geq 0 \quad (6)$$

which is of the form 3 where the contributions of the second-order tensor to both scalar and vectorial quantities are evidenced.

From the symmetry property of an isotropic system, constraints on phenomenological coefficients L_{ss}, $\mathbf{L}_{sv}$, $\mathbf{L}_{sa}^a$, $\mathring{\boldsymbol{L}}_{st(s)}$ follow. Each tensorial quantity $\boldsymbol{T}$ of n-th order transforms in

the following way under orthogonal transformation $\boldsymbol{A}$ (actually, each quantity that satisfies the following relation after orthogonal transformation is called a tensor of a n-th order),

$$\boldsymbol{T}'^{\overbrace{i\ldots l}^{n}} = \left(\det \boldsymbol{A}\right)^{\varepsilon} \sum_{r\ldots t} \underbrace{\boldsymbol{A}^{ir}\ldots\boldsymbol{A}^{lt}}_{n} \boldsymbol{T}^{\overbrace{r\ldots t}^{n}} \tag{7}$$

where $\det \boldsymbol{A} = \pm 1$, ε is equal to zero and one for polar and axial tensors, respectively. If the system has a symmetry property, then the effects of thermodynamic force will have the same symmetry property on thermodynamic fluxes. This means that the considered orthogonal transformation $\boldsymbol{A}$ does not modify the phenomenological tensors

$$\boldsymbol{L}' = \boldsymbol{L}$$

We may now proceed in the classical way, considering all types of orthogonal transformations and deducing constraints on phenomenological coefficients. First, the isotropic system is invariant under an inversion. In this case, the relation describing the transformation 7 gives:

$$\boldsymbol{T}'^{\overbrace{i\ldots l}^{n}} = (-1)^{\varepsilon}(-1)^{n}\boldsymbol{T}^{\overbrace{i\ldots l}^{n}} = (-1)^{n+\varepsilon}\boldsymbol{T}^{\overbrace{i\ldots l}^{n}}$$

since the determinant of $\boldsymbol{A} = -1$. From here, it follows that in the case of an odd coefficient $(n + \varepsilon)$ the phenomenological coefficient must vanish. In the case of polar tensors, $\varepsilon = 0$, this leads to $\mathbf{L}_{sv} = 0$ $(n = 1)$, while for axial tensors, $\varepsilon = 1$, we produce no constraint on the coefficient in 4. Nevertheless, the axial vector of phenomenological coefficients $\mathbf{L}^{a}_{sa}$ also vanishes from the symmetric property of an isotropic system under arbitrary rotation $\boldsymbol{R}$, $\det \boldsymbol{R} = 1$. Such transformation leads to the following:

$$(\mathbf{L}^{a}_{sa})' = \boldsymbol{R}\mathbf{L}^{a}_{sa} = \mathbf{L}^{a}_{sa}$$

which can be satisfied only when $\mathbf{L}^{a}_{sa} = 0$.

Moreover, the coefficient $\boldsymbol{L}_{st}$ has to be zero as well. To prove this, we recall that any scalar quantity does not change under orthogonal transformation. Since, for arbitrary vectors $\mathbf{a}$, $\mathbf{b}$, the inner product,

$$\boldsymbol{L}_{st}:(\mathbf{a}^{T}\mathbf{b})$$

is a scalar quantity ($\mathbf{a}^{T}\mathbf{b}$ is a dyadic product of vectors $\mathbf{a}$,$\mathbf{b}$), the following must hold:

$$\boldsymbol{L}_{st}:(\mathbf{a}^{T}\mathbf{b}) = \boldsymbol{L}'_{st}:(\mathbf{a}'^{T}\mathbf{b}') = \boldsymbol{L}_{st}:(\mathbf{a}'^{T}\mathbf{b}')$$

because, in an isotropic system, $\boldsymbol{L}_{st}$ is invariant under arbitrary rotation $\boldsymbol{R}$. If we conceive the product $\boldsymbol{L}_{st}:(\mathbf{a}^{T}\mathbf{b})$ as a function of vectors $\mathbf{a}$ and $\mathbf{b}$, then it represents a bilinear function in $\mathbf{a}$ and $\mathbf{b}$. And, as demonstrated, after transformation $\boldsymbol{R}$ it becomes a bilinear form in $\mathbf{a}'$ and $\mathbf{b}'$, but with the same coefficients. This means that the bilinear expression $\boldsymbol{L}_{st}:(\mathbf{a}^{T}\mathbf{b})$ has to be a function of the bilinear invariants of vectors $\mathbf{a}$ and $\mathbf{b}$. Since the only invariant of this kind is the trace of dyadic product $(\mathbf{a}^{T}\mathbf{b})$, which is equal to $(\mathbf{a}\cdot\mathbf{b})$, it allows us to write:

$$\boldsymbol{L}_{st}:(\mathbf{a}^{T}\mathbf{b}) = L_{st}(\mathbf{a}\cdot\mathbf{b})$$

where L_{st} is a scalar. However, it then follows that tensor $\boldsymbol{L}_{st}$ has to be of the form,

$$\boldsymbol{L}_{st} = L_{st}\boldsymbol{U}$$

Moreover, since $\boldsymbol{L}_{st}$ now has a zero trace, it is proved that $\boldsymbol{L}_{st} = 0$.

We may conclude the following:

$$J_s = L_{ss}X_s + \mathbf{L}_{sv}\cdot\mathbf{X}_v + \mathbf{L}^{a}_{sa}\cdot\mathbf{X}^{a}_{a} + \mathring{\boldsymbol{L}}_{st(s)}:\mathring{\boldsymbol{X}}_{t(s)} = L_{ss}X_s$$

which is a mathematical formulation of the Curie principle for a scalar thermodynamic force, stating that only dissipative processes of the same tensorial order may influence each other in an isotropic system (see the classical thermodynamic literature, e.g., refs 21−23). From the above actioned retrieval of this principle, we may formulate it more precisely: a second-order tensor may influence the scalar process, but only through its invariant (as in relation 6); a symmetric traceless second-order tensor does not have any influence on scalar quantities (it was proven that $\boldsymbol{L}_{st} = 0$).

In the particular case of a scalar flux, the rate of chemical reaction and a second-order tensor, $(\nabla\boldsymbol{v})$, we have the following:

$$\begin{aligned} r_{\alpha} &= \left(L_{s_1}\mathscr{A}_{\alpha} + \tilde{L}_{s_2}\frac{1}{3}\mathrm{tr}(\nabla\boldsymbol{v})\right) + \mathbf{L}_{sa}(\nabla\boldsymbol{v})_{(a)} + \\ &\quad \boldsymbol{L}_{st}\mathring{\boldsymbol{D}} = \left(L_{s_1}\mathscr{A}_{\alpha} + \tilde{L}_{s_2}\frac{1}{3}\mathrm{tr}(\nabla\boldsymbol{v})\right) \\ &= L_{s_1}\mathscr{A}_{\alpha} + L_{s_2}\boldsymbol{D}^{(1)} \end{aligned} \tag{8}$$

where the influence of one of the invariants of the second-order tensor $(\nabla\boldsymbol{v})$ or $\boldsymbol{D}$ on the chemical reaction rate is evidenced.

The Scalar Quantity $\boldsymbol{D}^{(3)}$ and Shear Rate $\boldsymbol{D}^{(2)}$. We may use a very similar approach when we would like to study the influence of shear rate $D^{(2)}$ on a reaction rate r_{α} instead of rate of volume variation $D^{(1)}$. However, there are several differences that will bring us to the aforementioned conclusion.

First, the decomposition of tensor $\nabla\boldsymbol{v}$ has to be carried out,

$$\begin{aligned} \nabla\boldsymbol{v} = \frac{1}{3}D^{(2)}\boldsymbol{U} + \tilde{\boldsymbol{T}} = \frac{1}{3}D^{(2)}\boldsymbol{U} + \tilde{\boldsymbol{T}}_{(a)} + \tilde{\boldsymbol{T}}_{(s)} = \\ \frac{1}{3}D^{(2)}\boldsymbol{U} + (\nabla\boldsymbol{v})_{(a)} + \left(\boldsymbol{D} - \frac{1}{3}D^{(2)}\boldsymbol{U}\right) \end{aligned} \tag{9}$$

where $\tilde{\boldsymbol{T}}$ is not traceless and again $\boldsymbol{D}$ is the symmetric part of $(\nabla\boldsymbol{v})$. Further, let us denote the symmetric part by $\hat{\boldsymbol{D}}$. Then,

$$\widehat{\boldsymbol{D}} = \left(\boldsymbol{D} - \frac{1}{3}D^{(2)}\boldsymbol{U}\right) = \mathring{\boldsymbol{D}} + \frac{1}{3}(D^{(1)} - D^{(2)})\boldsymbol{U} \tag{10}$$

Thus again, we can record entropy production and, consequently, the phenomenological relation. Namely, for the scalar flux we have

$$J_s = L_{ss}X_s + \mathbf{L}_{sv}\cdot\mathbf{X}_v + \mathbf{L}^{a}_{sa}\cdot\mathbf{X}^{a}_{a} + \boldsymbol{L}_{st(s)}:\boldsymbol{X}_{t(s)} \tag{11}$$

which is similar to the form of scalar flux for $D^{(1)}$ 4, but in this case the second-order tensor is not traceless: $\boldsymbol{X}_{T(s)} = \hat{\boldsymbol{D}} = \mathring{\boldsymbol{D}} + (1/3)(D^{(1)} - D^{(2)})\boldsymbol{U}$. Furthermore, coefficient $\boldsymbol{L}_{st(s)}$ is now of the same character as the symmetric tensor $\boldsymbol{X}_T$, which means that tensor $\boldsymbol{L}_{st(s)}$ is symmetric but not traceless.

For the same reasons as in the case with $D^{(1)}$, the phenomenological coefficients $\mathbf{L}_{sv} = \mathbf{L}^a_{sa} = 0$ and

$$\boldsymbol{L}_{st} = L_{st}\boldsymbol{U}$$

However, now, since $\boldsymbol{L}_{st(s)}$ has a nonzero trace, the conclusion that $\boldsymbol{L}_{st} = 0$ does not hold. If we substitute these findings in the phenomenological relation 11, then we obtain, as in eq 8:

$$\begin{aligned} r_\alpha &= (L_{s_1}\mathscr{A}_\alpha + \tilde{L}_{s_2}D^{(2)}) + \mathbf{L}_{sa}(\nabla\boldsymbol{v})_{(a)} + \boldsymbol{L}_{st}\left(\boldsymbol{D} - \frac{1}{3}D^{(2)}\boldsymbol{U}\right) \\ &= (L_{s_1}\mathscr{A}_\alpha + \tilde{L}_{s_2}D^{(2)}) + L_{st}\frac{1}{3}(D^{(1)} - D^{(2)}) \\ &= L_{s_1}\mathscr{A}_\alpha + L_{s_2}D^{(2)} + L_{s_3}D^{(1)} \end{aligned} \tag{12}$$

Exactly the same method can be used for $D^{(3)}$

$$\begin{aligned} r_\alpha &= (L_{s_1}\mathscr{A}_\alpha + \tilde{L}_{s_2}D^{(3)}) + \mathbf{L}_{sa}(\nabla\boldsymbol{v})_{(a)} + \boldsymbol{L}_{st}\left(\boldsymbol{D} - \frac{1}{3}D^{(2)}\boldsymbol{U}\right) \\ &= (L_{s_1}\mathscr{A}_\alpha + \tilde{L}_{s_2}D^{(3)}) + L_{st}\frac{1}{3}(D^{(1)} - D^{(3)}) \\ &= L_{s_1}\mathscr{A}_\alpha + L_{s_2}D^{(3)} + L_{s_3}D^{(1)} \end{aligned} \tag{13}$$

Discussion and Conclusions

From the three derived phenomenological relations for the rate of chemical reactions r_α 8, 12, and 13, we have established that the only scalar quantity related to the rate of deformation tensor $\boldsymbol{D}$ (or $\nabla\boldsymbol{v}$) that cannot be neglected is the rate of volume dilatation $D^{(1)}$.

For this reason, we may discuss the importance of the impacts of all possible types of mechanical stimulation on the rate of chemical reaction. The CIT theory used leads us to the conclusion that the rate of volume variation $D^{(1)}$ is the most important mechanical stimulus driving the chemical reaction, since, although only the influence of the invariant $D^{(2)}$ (or $D^{(3)}$) was assumed, the rate of volume variation $D^{(1)}$ does indeed impact on the chemical reaction rate (see eq 12).

However, this conclusion will probably be valid only at the tissue level (larger scale) because, at the cellular level, mechanical stimulation may trigger directly a cascade of chemical processes which actualise mechanotransduction (see Introduction). Moreover, application of the used linear theory of nonequilibrium thermodynamics is restricted to vicinity of equilibrium.[23] It can be used in majority of cases of bone remodelling since bone is found in equilibrium in physiological (healthy) state and adaptation of bone to changes in environment occurs slowly.

A new approach based on a mesoscopic description of nonequilibrium thermodynamics has recently been proposed, which may be used even in mesoscopic levels and for processes beyond the framework of CIT. Pagonabarraga et al. were able to obtain a nonlinear relation between affinity and reaction rate when a linear relation between flux and force was assumed in the internal space, and thus avoiding the limitation of the usage of CIT for relaxation phenomena.[24] In the Feature article,[25] the framework of MNET (mesoscopic nonequilibrium thermodynamics) with its applications and limitations is presented. When admitting further degrees of freedom (not yet equilibrated) that have influence on the overall dynamics of the system, even in a case far from equilibrium where linear laws do not hold, the evolution of the system can be described by Fokker−Planck equations for the evolution of the probability density of the degrees of freedom. This is possible because the evolution in time mimics a generalized diffusion process in the space of mesoscopic variables, where the linear theory has wide domain of validity. The possibility of using this theory for extending the presented result to a wider domain of applicability will be a subject of further research since straightforward application of MNET is not possible since the assumption of locality in mesoscopic variables is being used when establishing linear relationships between fluxes and forces.

The above-mentioned result—that the rate of volume variation is the essential mechanical stimulus—is in accordance with observations from equilibrium thermodynamics. For the differential of specific Gibbs energy, g, it holds that

$$\mathrm{d}g = -s\,\mathrm{d}T + \frac{1}{\rho}\,\mathrm{d}p - \sum_{\alpha=1}^{s}\mathscr{A}_\alpha\,\mathrm{d}\xi_\alpha$$

from where it follows

$$\left(\frac{\partial\mathscr{A}_\alpha}{\partial_P}\right)_{T,\xi_\alpha} = -\left(\frac{\partial\frac{1}{\rho}}{\partial\xi_\alpha}\right)_{T,p,\xi_{\alpha'}}$$

It is evident that, even in equilibrium thermodynamics, the driving force of chemical reaction, affinity $\mathscr{A}_\alpha$ changes with volume variation $1/\rho$. Without doubt, a certain change in volume (during an isothermal, isobaric process, and with other reactions α' in equilibrium) results in a change of affinity in a chemical reaction.

The aim of this work was to compare the importance of various mechanical stimulations on tissue remodelling because despite great advancements in the knowledge of mechanosensing and mechanotransduction, it is still not clear what type of mechanical stimulation is the most suitable. As Amin mentions in his recent review on the role of mechanical stimuli in bone, the primary mechanical factors that govern bone homeostasis remain a source of debate.[26] The essential role of mechanical stimulation is currently also being recognized in other fields of biology or medicine; for example, Sriram et al. suggest that dynamic mechanical stimuli enhance adaptive remodelling of condylar cartilage;[27] Tschumperlin et al. believe that (varying) mechanical stress contributes to the remodelling of the asthmatic airway;[28] and Seliktar et al. showed that dynamic mechanical stimuli is important even during tissue culture of tissue-engineered blood vessel constructs, where dynamic mechanical conditioning leads to an improvement in the properties of the constructs in terms of mechanical strength and histological organization.[29] Currently, in bone tissue, where the significance of dynamic mechanical stimulation was presumably first recognized, probably the most widely accepted hypothesis is that osteocytes are the most important mechanosensing cells in bone tissue and that osteocytes sense mechanical loading by the shear stress of fluid flow in canaliculi and lacunas, where they are located. This means that the shear rate would be the dominant mechanical stimulus. Sikavitsas cites several in vivo studies,

showing that osteocytes increase the expression of several factors after loading.[30] However, it should be noted that it is still not clear how osteocytes actually sense mechanical loading.[30,31] The first mentioned hypothesis is by fluid flow, which is exemplified by an experiment where 5 min after pulsating fluid flow (sheep, 0.5 Pa, 5 Hz) the prostaglandin levels significantly increased (prostaglandins are believed to be essential in the transduction of mechanical stimuli). This would also support the importance of microcracks in the bone remodelling process. Microcracks cause an increase in permeability of canaliculi and lower fluid drag, and are considered an important local factor influencing the triggering and running of bone remodelling in specific areas by, according to one theory, the rupture of osteocyte processes which result in upregulation of RANKL production by osteocytes.[32] Kurata et al. revealed a possible translation of mechanical stimuli into biochemical factors, observing that microcrack creation and propagation caused a higher expression of RANKL, which promotes osteoclastogenesis.[33] Another theory posits that mechanical loading will cause the higher proliferation of osteoblasts and an increase in mineralization. However, there is another possibility of mechanosensing by osteocytes, directly through the cytoskeleton with the aid of integrin interaction. This hypothesis is exemplified by an experiment where the expression of osteopontin mRNA was increased 4×, 9 h after the osteoblasts were exposed to a *dynamic* spatially uniform biaxial strain (0.25 Hz for 2 h). Ingber also believes that the extracellular matrix itself, prior to fluid flow, is more important for mechanosensing.[34] Klika and Maršík demonstrated that the bone remodelling process may be described and simulated when considering the rate of volume variation as the only mechanical stimulation and neglecting shear rate.[35,19,20,36] As was mentioned, tissues are exposed to all variety of mechanical factors: straining, shear, pressure, and even dynamic electric fields, and the results found in this work indicate that the volume variation rate is the most important mechanical stimulus driving the processes in them.

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Nomenclature

General Notation

Notation	Meaning
$\boldsymbol{T}$	a tensor
T^{ij}	*ij*-th component of a second-order tensor (spatial coordinates)
$\boldsymbol{v}$	a vector
v^i	*i*-th component of a vector (spatial coordinate)
c	a scalar
tr $\boldsymbol{T}$	trace of a tensor
X_i	a thermodynamic force
J_i	a thermodynamic flux
$\boldsymbol{U}$	unitary tensor
$\boldsymbol{T}_{(a)}$	antisymmetric part of a tensor
$\boldsymbol{T}_{(s)}$	symmetric part of a tensor
$\mathring{\boldsymbol{T}}_{(s)}$	symmetric and traceless part of a tensor
$T^{(1)}$, $T^{(2)}$, $T^{(3)}$	invariants of a tensor
$\boldsymbol{T}'$	a tensor after orthogonal transformation

Used Notation of Quantities

$\boldsymbol{\sigma}(S)$ [J·s^{-1}·m^{-3}·K^{-1}]	entropy production density
$\mathbf{j}_q$ [J·m^{-2}·s^{-1}]	heat flux density
T [K]	thermodynamic temperature
$\mathbf{j}_{\mathbf{D}i}$ [kg·m^{-2}·s^{-1}]	diffusion flux density of *i*-th substance
μ_i [J·kg^{-1}]	chemical potential of *i*-th substance
$\mathbf{F}_i$ [N·kg^{-1}]	external volume force acting on *i*-th substance
$\boldsymbol{t}_{\mathrm{dis}}$ [Pa]	dissipative part of stress tensor
$\boldsymbol{v}$ [m·s^{-1}]	velocity of material point
r_α [kmol·m^{-3}·s^{-1}]	reaction rate of α-th reaction
$\mathscr{A}_\alpha$ [J·kmol^{-1}]	affinity of α-th reaction
ρ [kg·m^{-3}]	density
p [Pa]	static pressure (can be interpreted as a mechanical energy density)
$\boldsymbol{E}$ [1]	Lagrangian finite strain tensor
$\boldsymbol{D}$ [s^{-1}]	the rate of deformation tensor
$\mathbf{u}$ [m]	displacement vector
x_j [m]	spatial coordinate
$\mathring{\boldsymbol{D}}$ [s^{-1}]	symmetric and traceless part of tensor $\boldsymbol{D}$
g [J·kg^{-1}]	specific Gibbs energy

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