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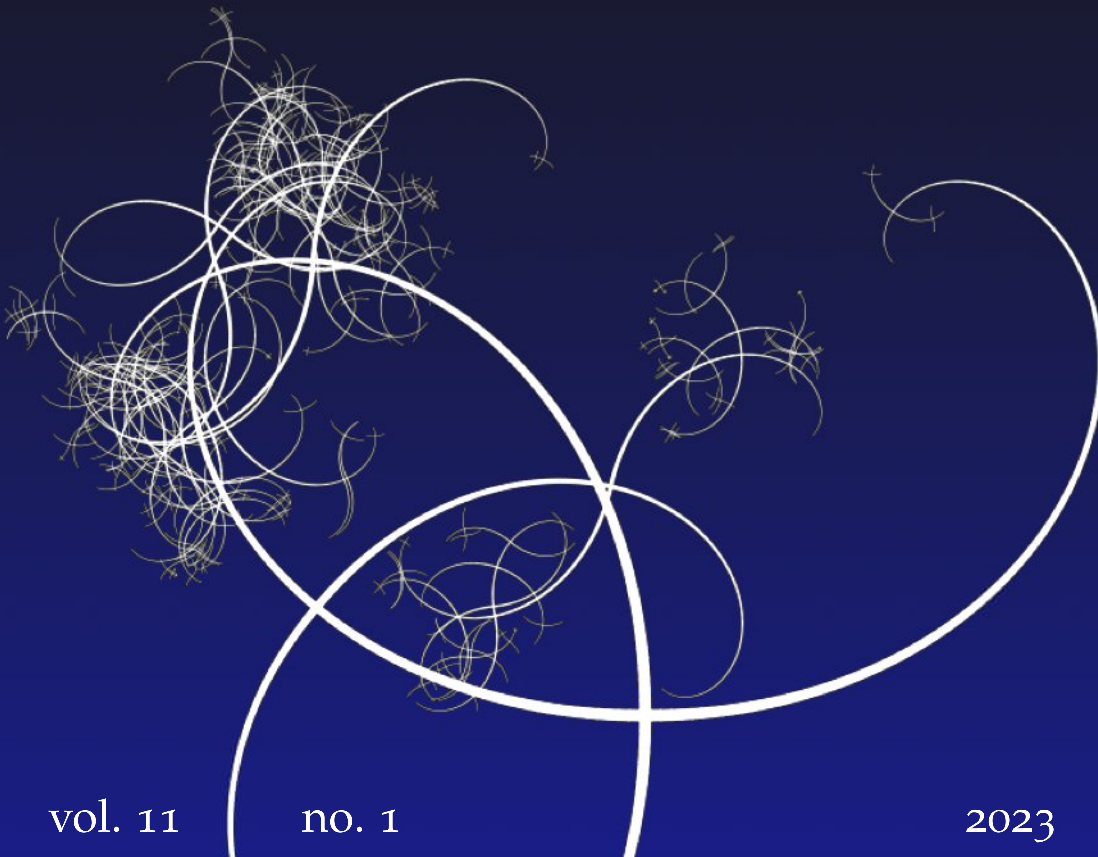

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Alfio Grillo and Salvatore Di Stefano

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AN A POSTERIORI APPROACH TO THE MECHANICS OF VOLUMETRIC GROWTH

ALFIO GRILLO AND SALVATORE DI STEFANO

This work focuses on the study of volumetric growth, i.e., the branch of biomechanics that investigates the variation of mass of biological systems, modeled as continuous media. Our purpose is to analyze in detail a perspective of growth, taken from the literature, that follows the paradigm of analytical mechanics. The analysis unfolds through (i) the introduction of suitable structural kinematic descriptors associated with growth; (ii) the identification of generalized forces dual to the virtual variations of such descriptors; (iii) the formulation of the principle of virtual work; and (iv) the establishment of a constitutive framework capable of capturing the phenomenology of interest. Within this setting, we determine the growth law of the problem at hand as a consequence of the dynamics of its structural descriptors. Accordingly, we term the growth law obtained this way the "a posteriori growth law", and we call the resulting overall approach the "a posteriori approach".

1. Introduction

Biological growth is a phenomenon that involves a heterogeneous multitude of processes, which embrace genetic and epigenetic events, characterized by chemical, physical and mechanical features, and whose course depends essentially on the specific system in which it occurs, be it a bone, skin, an aggregate of cells or a tumor, to mention a few [Taber 1995]. These aspects are already sufficient to realize why a correct description of growth requires us to conceive models with diverse rationales. Indeed, even specializing the growth models to the case of tumor growth, as for this work, is difficult: the variety of existing tumors, their peculiarities, their property of developing by following multiform processes, and the necessity for a detailed phenomenological characterization of their evolution make it very arduous to conceive an omni-comprehensive modeling strategy. However, in spite of these difficulties, it is possible to formulate approaches that are paradigmatic, in the sense

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that they rely on a unified logical pattern, while preserving the flexibility needed to capture the phenomenology of interest.

In this work, with the aim of determining suitable growth laws, i.e., representations of the mass source and sink of the biological systems at hand (in fact, mainly tumors), we consider approaches based on continuum mechanics, and we group them in two categories. We call "a priori approaches" the methodologies in which the growth laws are deduced phenomenologically and imposed from the outset (see, for example, [Ambrosi and Preziosi 2002; 2009; Ambrosi and Mollica 2002; Mascheroni et al. 2016; 2018]). In this case, the modeler is a careful observer of the biological phenomenology related to growth, and is committed to translate this phenomenology into the language of mechanics, with particular care for the coupling of mechanics with the tumor's biochemistry. In the other procedures, instead, which we call "a posteriori approaches", the modeler is pledged to formalize growth at least as a chemo-mechanical process, suitably immersed in the biological context, and determines the growth laws a posteriori, as a consequence of the tumor's overall dynamics (see, e.g., [Grillo et al. 2019a; Licari 2021]). Within the framework of [DiCarlo and Quiligotti 2002; DiCarlo 2005], this procedure is based on the introduction of *nonconventional forces* capable of describing the chemo-mechanical coupling and any other relevant aspect at the basis of growth [Grillo et al. 2019a; Licari 2021]. In particular, this coupling should be able, on the one hand, to capture the contrasting role that compressive mechanical stress has on cell replication (see, for example, [Helmlinger et al. 1997; Chaplain et al. 2006; Stylianopoulos et al. 2012; Jain et al. 2014]), and, on the other hand, to recast the tumor's biochemistry into mechanical interactions (see, for example, [DiCarlo and Quiligotti 2002; DiCarlo 2005]). Also the works [Epstein and Maugin 2000; Epstein and Elżanowski 2007], although chiefly focused on the thermomechanical aspects of growth, can be framed within the a posteriori approaches, since the growth laws determined therein are obtained after the dynamics of the considered growing medium is solved. To do this, the "traditional" thermomechanic framework of continuum mechanics is enriched with the introduction of *"noncompliant"* sources and sinks of mass, momentum, energy and entropy (see [Epstein and Maugin 2000; Goriely 2017; Epstein and Elżanowski 2007]). Epstein and Elżanowski [2007], while presenting a review on growth, provide a critique to the methodology based on the introduction of the "nonconventional forces" discussed above and in the sequel.

It is important to emphasize that the main difference between the a priori approaches and the a posteriori ones is methodological. The former make the growth law known in advance and determine the system's dynamics accordingly. The latter, instead, determine the system's dynamics, *and* the growth law, by predicting specific interactions related to growth. These, in turn, manifest themselves either through an enriched kinematics and the above mentioned nonconventional forces, if the theory adopted is based on the principle of virtual work [DiCarlo and Quiligotti 2002], or through the *"noncompliant"* sources and sinks adopted by [Epstein and Maugin 2000; Epstein and Elżanowski 2007], if the theory relies on an extension of the classical thermodynamics of continua (see also [Loret and Simões 2005; Goriely 2017]). In addition, it should be noted that, although the a priori approaches have been typically framed within the classical thermodynamics of continua, they can also be cast within the paradigmatic framework of the principle of virtual work. Indeed, we have recently formulated an a priori approach by exploiting the principle of virtual work, and treating the growth law as a nonholonomic, kinematic constraint [Grillo and Di Stefano 2023b; Grillo and Di Stefano 2023c]. In the sequel, however, we concentrate on an a posteriori approach, initially developed in [Grillo et al. 2019a; Licari 2021] by exploring the theory of growth of [DiCarlo and Quiligotti 2002], and, as a step forward, we show how it can be employed to improve the definition of physically sound growth laws through the selection of appropriate nonconventional forces.

For our purposes, we define first the kinematics of growth. Hence, following [DiCarlo and Quiligotti 2002], we introduce the Bilby–Kröner–Lee decomposition of the tumor's deformation gradient tensor [Rodriguez et al. 1994], and we treat the anelastic factor of this decomposition as a full-fledged kinematic descriptor of the theory. This factor is a second-order tensor field and is referred to as *growth tensor*. The dynamics of the tumor is determined by two coupled equations, endowed with initial and boundary conditions. One of these equations is the "classical" linear momentum balance, while the other one is a force balance involving generalized forces, hereafter denoted by $\boldsymbol{Y}$ and $\boldsymbol{Z}$, defined by duality with the virtual variations of the growth tensor [DiCarlo and Quiligotti 2002]. Both equations are obtained through the principle of virtual work, and the problem is closed by establishing a constitutive framework sufficiently flexible to describe the coupling between the mechanics of the tumor and the interactions stemming from the presence of chemical substances termed "nutrients". Within this context, and just as one would do for characterizing the external forces featuring in the "classical" momentum balance law, we define the external generalized force $\boldsymbol{Z}$ on the basis of phenomenological observations. We emphasize, however, that neither a priori assumptions on the growth tensor nor phenomenological hypotheses on the growth law are supplied. Indeed, both an assumption on the growth tensor and a phenomenological hypothesis on the growth law would imply we are imposing a condition on a kinematic entity, which amounts to defining a constraint. Rather, the growth tensor and the growth law are manifestations of the tumor's dynamics (although no simulations are performed in this work), which account both for chemical interactions and for the evolution of the *"material inhomogeneities"* induced by growth (in the jargon of [Epstein and Maugin 2000]).

While a comparison between an a priori approach to growth and the approach shown hereafter is addressed by [Grillo and Di Stefano 2023a], in which numerical simulations are performed (a preliminary study of the a posteriori approach has also been conducted by [Licari 2021], following an idea proposed by [Grillo et al. 2019a]), the main results of our current research can be summarized as follows:

(a) By taking some suggestions from [DiCarlo 2005], we highlight the importance of the nonconventional external force dual to the virtual variations of the growth tensor. This force constitutes the basis of the a posteriori approach formulated in the sequel, since it is viewed as a manifestation of the body's chemical and mechanical interactions.

(b) After introducing the dissipative part of the internal force dual to the virtual variations of the growth tensor, we present a detailed study of the constitutive representation of this force.

(c) Although the importance of the Eshelby stress tensor has already been pointed out in several publications on growth mechanics (see, e.g., [Epstein and Maugin 2000; Garikipati et al. 2004; Loret and Simões 2005; Ambrosi and Guana 2007; Grillo et al. 2012]), we highlight it and contextualize it in our approach.

(d) We show how the growth law is determined, and we put emphasis on the physical meaning of each term that contributes to its identification.

The main results of this work are interpretative, and are meant to build connections between different perspectives of the mechanics of growth, with the purpose of clarifying the physics underlying each perspective. Finally, we remark that, although tumor growth is the main focus of our work, both the a posteriori and the a priori approach, being paradigmatic, can be adapted to other types of biological growth and, suitably generalized, also to other biological processes (e.g., remodeling).

2. Mass balance, growth laws and the Bilby–Kröner–Lee decomposition

For the purposes of our work, a growing tissue or tumor is modeled as a monophasic, solid continuum body. Although this is a poor representation of a biological medium, which should be regarded, at least, as a mixture of cells, extracellular matrix, and interstitial fluid, the considered picture may still be able to convey some fundamental aspects of the chemo-mechanical coupling that characterizes growth.

With respect to the body's reference placement $\mathscr{B} \subset \mathscr{S}$, where $\mathscr{S}$ is the three-dimensional Euclidean space, the local form of the mass balance reads

$$\dot{\varrho}_{\mathrm{R}} = J r_{\gamma} \quad \text{in } \mathscr{B} \times [t_{\mathrm{in}}, t_{\mathrm{fin}}], \tag{1}$$

where ϱ_{R} is the body's mass density expressed per unit volume of $\mathscr{B}$, $J := \det \boldsymbol{F} > 0$ is the determinant of the deformation gradient tensor $\boldsymbol{F}$, r_{γ} accounts for the gain or loss of matter induced by growth, and $[t_{\mathrm{in}}, t_{\mathrm{fin}}] \subset \mathscr{I}$ is the interval of time over which the considered system is observed, with $\mathscr{I}$ being the time line [Marsden and

Hughes 1983]. As is standard in continuum mechanics, for each pair $(X, t) \in \mathscr{B} \times \mathscr{I}$, $\boldsymbol{F}(X, t) := T\chi(X, t)$ is the tangent map of the embedding $\chi(\cdot, t) : \mathscr{B} \to \mathscr{S}$, referred to as deformation.[1] For every $X \in \mathscr{B}$, there exists a unique point $x \in \mathscr{S}$ such that $x = \chi(X, t) \in \mathscr{S}$ [Marsden and Hughes 1983]. By definition, it holds that $\boldsymbol{F}(X, t) : T_X\mathscr{B} \to T_x\mathscr{S}$, where $T_X\mathscr{B}$ is the tangent space of $\mathscr{B}$ at $X \in \mathscr{B}$, and $T_x\mathscr{S}$ is the tangent space of $\mathscr{S}$ at $x = \chi(X, t) \in \mathscr{S}$. Note that $\mathscr{B}_t := \chi(\mathscr{B}, t)$ is the placement of the body at time t.

To describe the structural changes of the medium induced by its growth, we use the Bilby–Kröner–Lee (BKL) decomposition of the deformation gradient tensor, which we write as $\boldsymbol{F}(X, t) = \boldsymbol{F}_{\mathrm{e}}(X, t)\boldsymbol{K}(X, t)$, where $\boldsymbol{F}_{\mathrm{e}}(X, t)$ is the elastic part of $\boldsymbol{F}(X, t)$, and $\boldsymbol{K}(X, t)$ is its anelastic, growth related part. Tensor $\boldsymbol{K}$ is generally referred to as the *growth tensor*. Both $\boldsymbol{F}_{\mathrm{e}}(X, t)$ and $\boldsymbol{K}(X, t)$ have strictly positive determinants $J_{\mathrm{e}}(X, t) := \det \boldsymbol{F}_{\mathrm{e}}(X, t) > 0$ and $J_{\boldsymbol{K}}(X, t) := \det \boldsymbol{K}(X, t) > 0$. For each $t \in [t_{\mathrm{in}}, t_{\mathrm{fin}}]$, $\boldsymbol{K}(X, t)$ maps $T_X\mathscr{B}$ into a vector space $\mathscr{N}_X(t)$, called the *natural* (or *relaxed*) state. Indeed, the elements of $\mathscr{N}_X(t)$ are associated with a stress-free state obtained by relaxing elastically the elements of $T_x\mathscr{S}$, with $x \in \mathscr{B}_t$, until a state of null stress is met. For a review on the BKL decomposition the reader is referred, e.g., to [Sadik and Yavari 2017], and, in the context of biomechanics, e.g., to [Rodriguez et al. 1994; Taber 1995].

By introducing the mass density in the body's natural state, denoted by ϱ_ν, we can write $\varrho_{\mathrm{R}} = J_{\boldsymbol{K}}\varrho_\nu$. Hence, by enforcing the condition $\dot{\varrho}_\nu = 0$, and recalling the identity $\dot{J}_{\boldsymbol{K}} = J_{\boldsymbol{K}} \operatorname{tr}(\boldsymbol{K}^{-1}\dot{\boldsymbol{K}})$, we find (see, for example, [Epstein and Maugin 2000; Lubarda and Hoger 2002])

$$\operatorname{tr}(\boldsymbol{K}^{-1}\dot{\boldsymbol{K}}) = R_\gamma \quad \text{with } R_\gamma := \frac{J\, r_\gamma}{J_{\boldsymbol{K}}\varrho_\nu}, \tag{2}$$

with R_γ defined in (2) being the reciprocal of a characteristic time, and r_γ representing a mass density per unit time. To avoid confusion, we remark that R_γ is not the Piola transform of r_γ, since, as reported in (2), $J r_\gamma$ is normalized with respect to $\varrho_{\mathrm{R}} = J_{\boldsymbol{K}}\varrho_\nu$. The expressions of r_γ and R_γ, which we refer to as *growth laws* from here on (cf. [Grillo and Di Stefano 2023b; Grillo and Di Stefano 2023c]), must encompass all the pieces of information that are needed, even at a minimal level, for describing the activation, progression, and deactivation of growth in the considered body. In turn, these pieces of information may be coded in phenomenological representations of r_γ or R_γ, or may be determined in a self-consistent manner. In harmony with the spirit of this work, we *do not* prescribe any growth law a priori. Rather, we compute a growth law a posteriori through (2), i.e., self-consistently, as a result of the evolution of the growth tensor $\boldsymbol{K}$, which, thus, defines R_γ by

[1] We recall that $\chi(\cdot, t) : \mathscr{B} \to \mathscr{S}$ is an embedding because, for every $t \in \mathscr{I}$, the associated map $\hat{\chi}(\cdot, t) : \mathscr{B} \to \chi(\mathscr{B}, t)$, defined by $\hat{\chi}(X, t) = \chi(X, t)$, for all $X \in \mathscr{B}$, is a diffeomorphism.

means of the identification $R_\gamma \equiv \mathrm{tr}(\boldsymbol{K}^{-1}\dot{\boldsymbol{K}})$ (see [Epstein and Maugin 2000; Grillo et al. 2019a; Licari 2021; Grillo and Di Stefano 2023a] for a similar procedure). To accomplish this task, we need first to determine the equation that governs the dynamics of $\boldsymbol{K}$. Following the line of thought put forward by [DiCarlo and Quiligotti 2002], this will be done in three steps:

(i) We regard $\boldsymbol{K}$ as a variable that describes the kinematics of the tumor's structural transformations brought about by its growth.

(ii) We introduce the virtual variations of $\boldsymbol{K}$, i.e., $\delta\boldsymbol{K}$, and identify the *generalized forces* dual to such variations.

(iii) By means of the principle of virtual work, we determine the dynamic equation sought for.

3. The a posteriori approach to growth

Following the ideas put forward by [Epstein and Segev 1980; Cermelli et al. 2001; DiCarlo and Quiligotti 2002], we adhere to the paradigmatic framework of the principle of virtual work to conduct the study of a growing medium and, in particular, of the set of equations governing its dynamics. To this end, we begin with a review of some parts of [DiCarlo and Quiligotti 2002]. Then, we present the initial and boundary value problem that arises from expanding their theory, and that yields the a posteriori approach discussed in the sequel. Finally, we summarize the constitutive laws assumed in our work to address tumor growth.

In accordance with the view discussed by [DiCarlo and Quiligotti 2002], and recently expanded by [Grillo et al. 2019a; Licari 2021; Grillo and Di Stefano 2023a; 2023b; 2023c], both χ and $\boldsymbol{K}$ are kinematic descriptors of the body under study, and they both contribute to determine its current configuration: χ determines the shape of the body, while $\boldsymbol{K}$ describes its internal structure. Coherently with this view, a virtual variation of the body configuration consists of a virtual change of χ *and* of $\boldsymbol{K}$. We refer to these virtual variations as *generalized virtual displacements*, and we denote them by $\delta\chi$ and $\delta\boldsymbol{K}$, so that, within the theory of [DiCarlo and Quiligotti 2002], the kinematic descriptors can be represented by the array $(\chi, \boldsymbol{F}, \boldsymbol{K}, \delta\chi, \mathrm{Grad}\,\delta\chi, \delta\boldsymbol{K})$. We highlight that, with this selection of kinematic descriptors, the model is of grade one in the deformation, as is the case for elastic materials, which are *"simple"* (in the terminology of [Eringen 1980]), and of *"grade zero"* in the growth tensor $\boldsymbol{K}$ (see [DiCarlo and Quiligotti 2002]). Accordingly, the gradients $\mathrm{Grad}\,\boldsymbol{K}$ and $\mathrm{Grad}\,\delta\boldsymbol{K}$ are not rated among the kinematic descriptors, nor is $\mathrm{Grad}\,\boldsymbol{K}$ regarded as a constitutive variable of the theory. Note that a similar framework has been recently adopted also by [Ciambella et al. 2022]. Clearly, there do exist generalizations to anelastic theories of higher order in $\boldsymbol{K}$, or in quantities related to it, for instance,

$J_{\boldsymbol{K}}$ (see, e.g., [Gurtin and Anand 2005; Javadi et al. 2020; Grillo and Di Stefano 2023b; Grillo and Di Stefano 2023c]), but these are out of the scopes of this work.

3.1. ***Principle of virtual work and field equations.*** Similarly to [DiCarlo and Quiligotti 2002], we introduce two generalized forces dual to $\boldsymbol{K}^{-1}\delta\boldsymbol{K}$, which we term *growth-conjugated* forces: one is classified as *internal*, and is indicated with $\boldsymbol{Y}$, while the other one is said to be *external*, is denoted by $\boldsymbol{Z}$, and represents the force referred to as "nonconventional" in this theory. Thus, we formulate the principle of virtual work as

$$\underbrace{\int_{\mathscr{B}} \boldsymbol{P} : \operatorname{Grad}\delta\chi}_{=:\mathcal{P}_{\mathrm{int,def}}} + \underbrace{\int_{\mathscr{B}} \boldsymbol{Y} : \boldsymbol{K}^{-1}\delta\boldsymbol{K}}_{=:\mathcal{P}_{\mathrm{int,g}}} = \underbrace{\int_{\mathscr{B}} \boldsymbol{f}\delta\chi + \int_{\partial_{\mathrm{N}}^{\chi}\mathscr{B}} \boldsymbol{\tau}\delta\chi}_{=:\mathcal{P}_{\mathrm{ext,def}}} + \underbrace{\int_{\mathscr{B}} \boldsymbol{Z} : \boldsymbol{K}^{-1}\delta\boldsymbol{K}}_{=:\mathcal{P}_{\mathrm{ext,g}}}. \quad (3)$$

Specifically, $\mathcal{P}_{\mathrm{int,def}}$ is the *internal* virtual work associated with the deformation and generated by the duality product between the first Piola–Kirchhoff stress tensor $\boldsymbol{P}$ and $\operatorname{Grad}\delta\chi$, while $\mathcal{P}_{\mathrm{ext,def}}$ is the *external* virtual work produced by the action of the body force $\boldsymbol{f}$ on $\delta\chi$ and by the action of the contact force $\boldsymbol{\tau}$ on the prolongation of $\delta\chi$ onto $\partial_{\mathrm{N}}^{\chi}\mathscr{B}$, the Neumann boundary of $\mathscr{B}$ with respect to χ. As is customary, we write the boundary of $\mathscr{B}$ as the disjoint union $\partial\mathscr{B} = \partial_{\mathrm{N}}^{\chi}\mathscr{B} \sqcup \partial_{\mathrm{D}}^{\chi}\mathscr{B}$, where $\partial_{\mathrm{D}}^{\chi}\mathscr{B}$ is the Dirichlet boundary for χ, and is the portion of $\partial\mathscr{B}$ on which χ is prescribed and, accordingly, $\delta\chi$ has to be null. Analogously to [DiCarlo and Quiligotti 2002], $\mathcal{P}_{\mathrm{int,g}}$ is the growth-related part of the *internal* virtual work generated by the action of $\boldsymbol{Y}$ on $\boldsymbol{K}^{-1}\delta\boldsymbol{K}$, and $\mathcal{P}_{\mathrm{ext,g}}$ is the growth-related *external* virtual work expended by $\boldsymbol{Z}$ on $\boldsymbol{K}^{-1}\delta\boldsymbol{K}$. We note that equations similar to (3), with the specification of the virtual work done by the contact forces onto $\partial_{\mathrm{N}}^{\chi}\mathscr{B}$, can be found in [Grillo et al. 2019b; Licari 2021; Grillo and Di Stefano 2023a; 2023b; 2023c], and refer to the presentation of the weak form of balance laws provided by [Hughes 1987].

Since (3) has to hold for *arbitrary* choices of $\delta\chi$ in $\mathscr{B}$ and on $\partial_{\mathrm{N}}^{\chi}\mathscr{B}$, and of $\boldsymbol{K}^{-1}\delta\boldsymbol{K}$ in $\mathscr{B}$, and upon prescribing $\chi = \chi_{\mathrm{b}}$ on $\partial_{\mathrm{D}}^{\chi}\mathscr{B}$, we arrive at the set of equations

$$\operatorname{Div}\boldsymbol{P} + \boldsymbol{f} = \boldsymbol{0} \quad \text{in } \mathscr{B}, \quad (4a)$$

$$\chi = \chi_{\mathrm{b}} \quad \text{on } \partial_{\mathrm{D}}^{\chi}\mathscr{B}, \quad (4b)$$

$$\boldsymbol{P}\boldsymbol{N} = \boldsymbol{\tau} \quad \text{on } \partial_{\mathrm{N}}^{\chi}\mathscr{B}, \quad (4c)$$

$$\boldsymbol{Y} - \boldsymbol{Z} = \boldsymbol{0} \quad \text{in } \mathscr{B}, \quad (4d)$$

with $\boldsymbol{N}$ being the field of conormals associated with $\partial\mathscr{B}$. Equations (4a)–(4d) are said to constitute the strong form of the boundary value problem (BVP) at hand. Initial conditions on χ and $\boldsymbol{K}$ will be supplied when the time derivatives of χ and $\boldsymbol{K}$ appear explicitly in (4a)–(4d), i.e., after completing the constitutive picture of the body and prescribing the external forces $\boldsymbol{f}$ and $\boldsymbol{Z}$.

Whereas (4a)–(4c) are well established in continuum mechanics, (4d) is not, although there exists a conspicuous branch of literature (see, e.g., [Gurtin 1996; Cermelli et al. 2001; Gurtin and Anand 2005]) for which equations of this type are natural consequences of the theoretical framework developed therein. In fact, because of its importance in the present setting, (4d) deserves special attention. In particular, to turn it into a dynamic equation for $\boldsymbol{K}$, the force $\boldsymbol{Y}$ must be related constitutively to $\boldsymbol{K}$ and $\dot{\boldsymbol{K}}$. On the other hand, when such constitutive relationships cannot be found, (4d) determines $\boldsymbol{Y}$, or one of its components, through the identity $\boldsymbol{Y} \equiv \boldsymbol{Z}$, provided that $\boldsymbol{Z}$ is defined [Cermelli et al. 2001]. This may occur, for instance, when the evolution of $\boldsymbol{K}$ is required to satisfy one or more constraints (see, for example, [Grillo and Di Stefano 2023b; 2023c]). Note also that, even in the case in which $\boldsymbol{Z}$ were assumed to be null, the resulting identity $\boldsymbol{Y} \equiv \boldsymbol{0}$ would not be trivial. Indeed, the essentially dissipative nature of the phenomenon under study implies that $\boldsymbol{Y}$ splits additively into the sum of a nondissipative part, that is, the Eshelby stress tensor, and a dissipative part, hereafter termed $\boldsymbol{Y}_{\mathrm{d}}$ (see (7c) below). Hence, if $\boldsymbol{Y}_{\mathrm{d}}$ can be obtained constitutively, the equation $\boldsymbol{Y} = \boldsymbol{0}$ can be turned into a dynamic equation for $\boldsymbol{K}$, whereas if $\boldsymbol{Y}_{\mathrm{d}}$ cannot be represented constitutively, it is determined by the negative of the Eshelby stress tensor (see, e.g., [Cermelli et al. 2001, for a similar situation in plasticity]).

We remark that the balance law (4d) reduces to the equality $\boldsymbol{Y} = \boldsymbol{Z}$ because growth is modeled here as a theory of grade zero in $\boldsymbol{K}$. However, if a theory of grade one in $\boldsymbol{K}$ were formulated (see, for example, [Gurtin and Anand 2005]), the principle of virtual work would call for a generalized stress dual to $\operatorname{Grad} \delta\boldsymbol{K}$, i.e., a third-order tensor field, and would allow for the introduction of some generalized external force, dual to $\delta\boldsymbol{K}$ and defined on a given portion of the body's boundary. In such a theory, the force balance (4d) would look like (4a) (up to the order of the tensor fields involved), and an additional Neumann boundary condition would be required.

To conclude, we mention that, although we are employing the principle of virtual work for studying growth, we are aware of criticisms to its application for this type of phenomena (see, e.g., [Epstein and Elżanowski 2007]). In this respect, two remarks are in order. On the one hand, the crux of what we call "a posteriori approaches" is the requirement that the growth law be computed after determining the dynamics of the growing body, rather than being imposed from the outset, as is done in the a priori approaches. In fact, as highlighted in Section 1, this goal can be achieved by formulating the problem at hand either within a theory grounded on the principle of virtual work [DiCarlo and Quiligotti 2002] or within a theory based on the "classical" balance laws, suitably augmented with *"noncompliant"* terms, as proposed by [Epstein and Maugin 2000; Epstein and Elżanowski 2007]. On the other hand, since the route that is to be followed depends ultimately on the philosophical belief of each author, we have opted for the paradigm of the principle of virtual work because it seems to us a rather natural context for framing the a posteriori approach. In our opinion, this is because the principle of virtual work treats $\boldsymbol{K}$ as a Lagrangian parameter of the model, exactly like χ, and, thus, it yields the dynamic equation associated with it, (4d), simultaneously with the balance of linear momentum, (4a). This setting, in turn, seems to suggest to solve the BVP (4a)–(4d) altogether and determine the growth law accordingly, whereas assigning the latter from the outset would amount to imposing a constraint. As anticipated in Section 1, this has been done elsewhere (see [Grillo and Di Stefano 2023b; 2023c]), but it seems to us less straightforward. Also, the presence of the force $\boldsymbol{Z}$, when it does not vanish, has a direct influence on the evolution of $\boldsymbol{K}$ and, thus, on $R_\gamma \equiv \operatorname{tr}(\boldsymbol{K}^{-1}\dot{\boldsymbol{K}})$.

3.2. ***Dissipation inequality.*** The search for constitutive laws for $\boldsymbol{Y}$, when it makes sense to look for them, should stick to the restrictions accounted for by the general theory of constitutive laws (see, for example, [Eringen 1980; Liu 2002]). The constitutive law for $\boldsymbol{Y}$ should comply with its being defined in conjunction with the BKL decomposition and with additional conditions that involve possible material symmetries [Ogden 1997]. Among the restrictions coming from the general theory, we focus on the compliance with the dissipation inequality, which we formulate by following the *"mechanical version of the second law"* of thermodynamics [Gurtin 1996], adapted to our context (see also [Cermelli et al. 2001]), that is,

$$\begin{aligned}\int_{\mathscr{R}} \mathcal{D}_{\mathrm{R}} &:= -\overline{\int_{\mathscr{R}} \Psi_{\mathrm{R}}}^{\boldsymbol{\cdot}} + \int_{\mathscr{R}} \boldsymbol{f}\boldsymbol{v} + \int_{\partial\mathscr{R}} (\boldsymbol{P}\boldsymbol{N})\boldsymbol{v} + \int_{\mathscr{R}} \boldsymbol{Z} : \boldsymbol{K}^{-1}\dot{\boldsymbol{K}} \\ &= -\overline{\int_{\mathscr{R}} \Psi_{\mathrm{R}}}^{\boldsymbol{\cdot}} + \int_{\mathscr{R}} \boldsymbol{P} : \dot{\boldsymbol{F}} + \int_{\mathscr{R}} \boldsymbol{Y} : \boldsymbol{K}^{-1}\dot{\boldsymbol{K}} \geq 0, \end{aligned} \tag{5}$$

where $\mathcal{D}_{\mathrm{R}}$ and Ψ_{R} are the dissipation density and the body's Helmholtz free energy density per unit volume of $\mathscr{B}$, respectively, and $\mathscr{R}$ is a time independent subregion of $\mathscr{B}$ (see [DiCarlo and Quiligotti 2002]). We remark that, while the last three terms on the right-hand side of (5) define the dissipation in terms of the power external to $\mathscr{R}$, the last two terms on the far right-hand side are obtained by equating the power external to $\mathscr{R}$ to the power internal to it, as a consequence of (3). Accordingly, the local form of (5) reads

$$\mathcal{D}_{\mathrm{R}} = -\dot{\Psi}_{\mathrm{R}} + \boldsymbol{P} : \dot{\boldsymbol{F}} + \boldsymbol{Y} : \boldsymbol{K}^{-1}\dot{\boldsymbol{K}} \geq 0. \tag{6}$$

By selecting $\boldsymbol{F}$, $\boldsymbol{K}$, and $\dot{\boldsymbol{K}}$ as independent constitutive variables, assuming the body to be hyperelastic, and performing the Coleman–Noll procedure, we can show that (6) admits the constitutive choices

$$\Psi_{\mathrm{R}} = \hat{\Psi}_{\mathrm{R}} \circ (\boldsymbol{F}, \boldsymbol{K}) = (\det \boldsymbol{K})[\hat{\Psi}_\nu \circ (\boldsymbol{F}\boldsymbol{K}^{-1})] = (\det \boldsymbol{K})\Psi_\nu, \tag{7a}$$

$$\boldsymbol{P} = \hat{\boldsymbol{P}} \circ (\boldsymbol{F}, \boldsymbol{K}) = \frac{\partial \hat{\Psi}_{\mathrm{R}}}{\partial \boldsymbol{F}} \circ (\boldsymbol{F}, \boldsymbol{K}) = (\det \boldsymbol{K})\Big(\frac{\partial \hat{\Psi}_\nu}{\partial \boldsymbol{F}\boldsymbol{K}^{-1}} \circ (\boldsymbol{F}\boldsymbol{K}^{-1})\Big)\boldsymbol{K}^{-\mathrm{T}}, \tag{7b}$$

$$\boldsymbol{Y} = \tilde{\boldsymbol{Y}} \circ (\boldsymbol{F}, \boldsymbol{K}, \dot{\boldsymbol{K}}, \mathcal{X}, \mathcal{T}) = \hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K}) + \tilde{\boldsymbol{Y}}_{\mathrm{d}} \circ (\boldsymbol{F}, \boldsymbol{K}, \dot{\boldsymbol{K}}, \mathcal{X}, \mathcal{T}), \tag{7c}$$

where $\Psi_\nu := \hat{\Psi}_\nu \circ (\boldsymbol{F}\boldsymbol{K}^{-1})$ is the Helmholtz free energy density per unit volume of the natural state of the medium, $\boldsymbol{H} := \hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K})$ is the Eshelby stress tensor[2]

$$\boldsymbol{H} = \hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K}) = \boldsymbol{K}^{\mathrm{T}} \left(\frac{\partial \hat{\Psi}_{\mathrm{R}}}{\partial \boldsymbol{K}} \circ (\boldsymbol{F}, \boldsymbol{K}) \right) = [\hat{\Psi}_{\mathrm{R}} \circ (\boldsymbol{F}, \boldsymbol{K})] \boldsymbol{I}^{\mathrm{T}} - \boldsymbol{F}^{\mathrm{T}} [\hat{\boldsymbol{P}} \circ (\boldsymbol{F}, \boldsymbol{K})], \quad (8)$$

and constitutes the *nondissipative* part of $\boldsymbol{Y}$, while $\boldsymbol{Y}_{\mathrm{d}} := \tilde{\boldsymbol{Y}}_{\mathrm{d}} \circ (\boldsymbol{F}, \boldsymbol{K}, \dot{\boldsymbol{K}}, \mathcal{X}, \mathcal{T})$ is the *dissipative* part of $\boldsymbol{Y}$. Finally, $\mathcal{X} : \mathscr{B} \times \mathscr{I} \to \mathscr{B}$ and $\mathcal{T} : \mathscr{B} \times \mathscr{I} \to \mathscr{I}$ are two auxiliary maps, such that $\mathcal{X}(X, t) = X$ and $\mathcal{T}(X, t) = t$, for all $(X, t) \in \mathscr{B} \times \mathscr{I}$, introduced to account for the explicit dependence of a given physical quantity on the points of $\mathscr{B}$ and on time [Marsden and Hughes 1983; Federico et al. 2019; Grillo and Di Stefano 2023b].

If the external forces $\boldsymbol{f}$ and $\boldsymbol{Z}$ are given, (7a)–(7c) and (8) are sufficient to close the BVP (4a)–(4d). In particular, (4d) becomes

$$\tilde{\boldsymbol{Y}}_{\mathrm{d}} \circ (\boldsymbol{F}, \boldsymbol{K}, \dot{\boldsymbol{K}}, \mathcal{X}, \mathcal{T}) + \hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K}) = \boldsymbol{Z}, \quad (9)$$

and manifests the coupling, referred to as *"Eshelbian coupling"* by [DiCarlo and Quiligotti 2002], among the Eshelby stress tensor, $\boldsymbol{Y}_{\mathrm{d}}$, and $\boldsymbol{Z}$.

The idea at the root of the a posteriori approach based on the principle of virtual work is that (4d), recast in the form of (9), is converted into a dynamic equation for $\boldsymbol{K}$, equipped with suitable initial conditions, and solved with (4a)–(4c) in order to determine χ and $\boldsymbol{K}$ itself. To do this, we start by defining $\boldsymbol{Z}$.

4. The generalized force Z

By adhering to the line of thought developed by [Gurtin 1996; Cermelli et al. 2001; DiCarlo and Quiligotti 2002], the existence of the external, growth-conjugated generalized force $\boldsymbol{Z}$ must be assumed from the outset as a logical consequence of the fact that $\boldsymbol{K}$ and $\boldsymbol{K}^{-1}\delta\boldsymbol{K}$ are declared as kinematic descriptors. In this respect, the presence of $\boldsymbol{Z}$ is allotted also in the absence of any experimental evidence and $\boldsymbol{Z}$ may also turn out to be null (see also the discussion on this issue in [Cermelli et al. 2001]). However, as pointed out by [DiCarlo 2005], in the biomechanical context the force $\boldsymbol{Z}$ may have a dominant contribution, since it may represent, at the scale of the tissue, interactions coming from lower scales, as could be the case for chemical cues.

[2]The transpose of the deformation gradient tensor is defined as $\boldsymbol{F}^{\mathrm{T}}(x, t) : T^*_x \mathscr{S} \to T^*_X \mathscr{B}$, where $T^*_x \mathscr{S}$ and $T^*_X \mathscr{B}$ are the spaces dual to $T_x \mathscr{S}$ and $T_X \mathscr{B}$, respectively, with $X = [\chi(\cdot, t)]^{-1}(x)$ and $x \in \mathscr{B}_t$ (cf. with the definition of "$\boldsymbol{F}^*(x)$" given by [Marsden and Hughes 1983, in Problem 3.1, at page 49]). Hence, in order to redefine $\boldsymbol{F}^{\mathrm{T}}$ as a function of the points of $\mathscr{B}$ and time, as in (8), one should write $\boldsymbol{F}^{\mathrm{T}} \circ (\chi, \mathcal{T})$, with $\mathcal{T} : \mathscr{B} \times \mathscr{I} \to \mathscr{I}$, such that $(X, t) \mapsto \mathcal{T}(X, t) = t$ [Marsden and Hughes 1983; Federico et al. 2019]. However, when compositions of this kind are clear from the context, we simply write $\boldsymbol{F}^{\mathrm{T}}$, with a slight abuse of notation, as in (8). The same considerations apply, with slight changes, to $\boldsymbol{F}^{-1}$, $\boldsymbol{F}_{\mathrm{e}}^{-1}$ and $\boldsymbol{F}_{\mathrm{e}}^{\mathrm{T}}$.

With respect to the growth model we are dealing with, in order to properly prescribe a definition for $\boldsymbol{Z}$, it is necessary to explicitly account for the evolution, within the tumor, of some chemical agents, referred to as *nutrients*. Hereafter, we denote by ω the concentration of such substances, e.g., oxygen or glucose, which activate the accretion of mass, deactivate it, or trigger mass resorption. Usually, the nutrients are assumed to obey a diffusion-reaction equation, which is discussed in detail in a separate work [Grillo and Di Stefano 2023a] dedicated to the numerical simulation of the theoretical setup presented here (see also [Licari 2021], for a preliminary numerical study on this topic). For the purposes of the present work, instead, we do not focus on the evolution of the nutrients, although such evolution is tacitly considered. However, apart from that, and in order to maintain our study at a minimal complexity, we do not account for the contributions of the dynamics of the nutrients to the overall dissipation of the system (see (6), in which such contributions are not reported). Still, such dynamics are dissipative, since they feature the exchanges of mass of the nutrients with the growing medium and a mass flux vector that is usually described by Fick's law of mass diffusion (see, e.g., [Ramírez-Torres et al. 2021], for possible generalizations).

In this work, we hypothesize that $\boldsymbol{Z}$ can be taken as a function $\hat{\boldsymbol{Z}}$ of $\boldsymbol{F}$, $\boldsymbol{K}$, ω, and $\operatorname{Grad}\omega$, i.e.,

$$\boldsymbol{Z} = \hat{\boldsymbol{Z}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \operatorname{Grad}\omega) := \tfrac{1}{3} J_{\boldsymbol{K}} [\hat{\Gamma} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)] \boldsymbol{I}^{\mathrm{T}} + \hat{\boldsymbol{Q}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \operatorname{Grad}\omega), \quad (10)$$

where the dependence on ω and $\operatorname{Grad}\omega$ accounts for the influence that the nutrients exert on the force that regulates the overall mass accretion or resorption in the considered tissue. In (10), $\hat{\Gamma} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)$ is a purely volumetric contribution, while $\hat{\boldsymbol{Q}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \operatorname{Grad}\omega)$ is a not necessarily deviatoric contribution, conceived with the purpose of generating preferred directions in the process of mass variation within the body. In more detail, since $\hat{\boldsymbol{Z}}$ has to induce the variation of mass in the tissue, we choose $\hat{\Gamma} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)$ as

$$\hat{\Gamma} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega) := \kappa_{\mathrm{a}} [\hat{\Gamma}_{\mathrm{a}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)] + \kappa_{\mathrm{r}} [\hat{\Gamma}_{\mathrm{r}} \circ \omega], \quad (11)$$

where $\kappa_{\mathrm{a}} > 0$ and $\kappa_{\mathrm{r}} < 0$ are constant-valued coefficients with physical dimensions of stress, while $\hat{\Gamma}_{\mathrm{a}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)$ and $\hat{\Gamma}_{\mathrm{r}} \circ \omega$ are dimensionless functions given by

$$\hat{\Gamma}_{\mathrm{a}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega) := \langle h_{\mathrm{a}} \circ \omega \rangle_+ \left[1 - \frac{\alpha \, \langle \hat{\wp} \circ (\boldsymbol{F}, \boldsymbol{K}) \rangle_+}{\sigma_{\mathrm{c}} + \langle \hat{\wp} \circ (\boldsymbol{F}, \boldsymbol{K}) \rangle_+} \right], \quad (12a)$$

$$\hat{\Gamma}_{\mathrm{r}} \circ \omega := \langle h_{\mathrm{r}} \circ \omega \rangle_+, \quad (12b)$$

with the auxiliary notation

$$h_{\mathrm{a}} \circ \omega := \frac{\omega - \omega_{\mathrm{cr}}}{\omega_{\mathrm{env}} - \omega_{\mathrm{cr}}}, \qquad h_{\mathrm{r}} \circ \omega := 1 - \frac{\omega}{\omega_{\mathrm{cr}}}, \qquad \omega_{\mathrm{env}} > \omega_{\mathrm{cr}}. \quad (13)$$

In the above equations, $\omega_{\rm cr}$ and $\omega_{\rm env}$ are constant-valued functions that return the threshold value of the nutrients' concentration for the activation of growth and the reference value of the concentration of the nutrients available in the tissue's environment (assuming that the tissue finds itself in a nutrient bath), respectively; α is a dimensionless, nonnegative material constant that weighs the influence of stress on growth; $\sigma_{\rm c}$ is a constant-valued material parameter returning a strictly positive characteristic stress; $\wp$ is a scalar measure of stress, taken, in our work, as the hydrostatic Cauchy pressure, defined by $\hat{\wp} \circ (\boldsymbol{F}, \boldsymbol{K}) := -\frac{1}{3} \operatorname{tr}[\hat{\boldsymbol{\sigma}} \circ (\boldsymbol{F}, \boldsymbol{K})]$, with $\boldsymbol{\sigma}$ being the Cauchy stress tensor, and $\langle \cdot \rangle_+$ an operator such that $\langle a \rangle_+ := \frac{1}{2}(a + |a|)$, for $a \in \mathbb{R}$ [Mascheroni et al. 2016; 2018; Di Stefano et al. 2018; Grillo et al. 2019b]. Note that, at this stage, the possible dependence of the constitutive function of stress $\hat{\boldsymbol{\sigma}}$ on preferred directions, as is the case for anisotropic materials, and the influence of such preferred directions on $\boldsymbol{Z}$ are tacitly included. However, in this work, we consider only isotropic elastic materials, for the sake of simplicity. Note also that a definition of $\boldsymbol{Z}$ simpler than the one proposed in (10), with a different definition of $\Gamma := \hat{\Gamma} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)$, and a constant and deviatoric tensor $\boldsymbol{T}$ in lieu of $\hat{\boldsymbol{Q}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \operatorname{Grad} \omega)$, has been used in a preliminary work of ours whose main numerical results have been summarized by [Licari 2021].

We emphasize that the definitions in (10)–(13) have been obtained by "peeking" some growth laws provided a priori and on phenomenological basis in publications that follow an approach opposite to the one adopted here (see, for example, [Ambrosi and Preziosi 2002; 2009; Mascheroni et al. 2016; 2018; Agosti et al. 2018]). Yet, we have taken these laws, and have adapted them to our context, in order to benefit from the phenomenological information encoded in them. An example of such growth laws, slightly modified from [Mascheroni et al. 2016; 2018], is given by

$$\begin{aligned} R_\gamma \equiv R_{\gamma(\rm ph)} &:= \hat{R}_{\gamma(\rm ph)} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega) \\ &= \zeta_{\rm a} \langle h_{\rm a} \circ \omega \rangle_+ \left[1 - \frac{\alpha \langle \hat{\wp} \circ (\boldsymbol{F}, \boldsymbol{K}) \rangle_+}{\sigma_{\rm c} + \langle \hat{\wp} \circ (\boldsymbol{F}, \boldsymbol{K}) \rangle_+} \right] - \zeta_{\rm r} \langle h_{\rm r} \circ \omega \rangle_+, \end{aligned} \tag{14}$$

where the subscript "(ph)" stands for "phenomenological" (see [Grillo and Di Stefano 2023b; 2023c]), $\hat{R}_{\gamma(\rm ph)} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)$ indicates the constitutive representation of $R_{\gamma(\rm ph)}$, while $\zeta_{\rm a}$ and $\zeta_{\rm r}$ are nonnegative constant-valued material coefficients having the physical dimensions of the inverse of the characteristic time scales associated with mass accretion (first summand of (14)) and resorption (second summand of (14)), respectively.

To complete the presentation of $\hat{\boldsymbol{Z}}$, we have to supply $\hat{\boldsymbol{Q}}$. For this purpose, we suggest that the distribution of nutrients within the body gives rise to preferred directions of its variation of mass. Hence, we take inspiration from the theory of (isotropic) dispersion in porous media (see, for example, [Bear and Bachmat 1990]), and we hypothesize the expression

$$\begin{aligned}\boldsymbol{Q} &:= \hat{\boldsymbol{Q}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \operatorname{Grad}\omega) \\ &= J_{\boldsymbol{K}} Q_{\nu\mathrm{t}} \|\operatorname{Grad}\omega\|_{\boldsymbol{C}^{-1}} \boldsymbol{I}^{\mathrm{T}} + J_{\boldsymbol{K}} [Q_{\nu\ell} - Q_{\nu\mathrm{t}}] \frac{\operatorname{Grad}\omega \otimes \boldsymbol{C}^{-1} \operatorname{Grad}\omega}{\|\operatorname{Grad}\omega\|_{\boldsymbol{C}^{-1}}},\end{aligned} \tag{15}$$

where $\boldsymbol{C}$ is the right Cauchy–Green deformation tensor, $\|\operatorname{Grad}\omega\|_{\boldsymbol{C}^{-1}}$ is given by

$$\|\operatorname{Grad}\omega\|_{\boldsymbol{C}^{-1}} = (\boldsymbol{C}^{-1} : \operatorname{Grad}\omega \otimes \operatorname{Grad}\omega)^{1/2}, \tag{16}$$

while $Q_{\nu\ell}$ and $Q_{\nu\mathrm{t}}$ denote the longitudinal and transversal "dispersivities" associated with the body's natural state. Note that, according to (15), the tensor-valued function $\hat{\boldsymbol{Q}}$ is continuous in each of its arguments, and, as it stands, it is undefined for $\operatorname{Grad}\omega = \boldsymbol{0}$. Yet, since the limit of $\hat{\boldsymbol{Q}}$ for $\operatorname{Grad}\omega \to \boldsymbol{0}$ tends towards the null tensor, uniformly with respect to its other arguments, $\hat{\boldsymbol{Q}}$ can be prolonged by continuity to $\operatorname{Grad}\omega = \boldsymbol{0}$ by setting it equal to the null tensor for this value of $\operatorname{Grad}\omega = \boldsymbol{0}$, i.e., $\hat{\boldsymbol{Q}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \boldsymbol{0}) = \boldsymbol{0}$.

Before closing this section, we remark that choosing the contribution to $\boldsymbol{Z}$ given by $\hat{\Gamma} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)$ as in (10)–(13) is *not* in contradiction with the a posteriori approach presented in this work, since it does not amount to imposing the growth law *before* solving the dynamics of $\boldsymbol{K}$. Indeed, we do not calculate $\boldsymbol{K}$ starting from (2), with R_γ set equal to $R_{\gamma(\mathrm{ph})}$. Rather, as discussed in Section 6, we determine $R_\gamma \equiv \operatorname{tr}(\boldsymbol{K}^{-1}\dot{\boldsymbol{K}})$ a posteriori, i.e., once $\boldsymbol{K}$ is solved (see Remark 2 below). In doing this, we do not intend to necessarily reobtain the expression of $R_{\gamma(\mathrm{ph})}$ given in (14), but we aim at maintaining the biological ideas supported by the literature. Clearly, we could have prescribed $\hat{\Gamma} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)$ also in other ways, although we have decided to imitate the definition of $R_{\gamma(\mathrm{ph})}$ stated in (14) because it proved to be successful in modeling tumor growth (see [Mascheroni et al. 2016; 2018]). In addition, to the best of our knowledge, it is still hard to find in the literature explicit and physically sound definitions of $\boldsymbol{Z}$, if abstraction is made of those that have been introduced by some authors for remodeling and rely on the concept of "target stress" (see, e.g., [Olsson and Klarbring 2008]). This issue is discussed with reference to (50).

5. The internal, generalized dissipative force $\boldsymbol{Y}_{\mathrm{d}}$

As anticipated in the previous section, the identification of the forces dual to $\delta\boldsymbol{K}$ is essential for encompassing the mechanical and biochemical information sufficient to yield phenomenologically sound growth laws. This applies both to $\boldsymbol{Z}$ and to $\boldsymbol{Y} = \boldsymbol{Y}_{\mathrm{d}} + \boldsymbol{H}$ (see (7c)). Since $\boldsymbol{H}$ and $\boldsymbol{Z}$ have been studied above, we focus here on $\boldsymbol{Y}_{\mathrm{d}}$.

If $\boldsymbol{Z}$ is written as in (10), the right-hand side of (9) depends on the value attained by ω, which, thus, acquires the meaning of a control parameter. This suggests to redefine the constitutive representation of $\boldsymbol{Y}_{\mathrm{d}}$ assumed in (7c) at least as $\boldsymbol{Y}_{\rm d} := \hat{\boldsymbol{Y}}_{\rm d} \circ (\boldsymbol{F}, \boldsymbol{K}, \dot{\boldsymbol{K}}, \omega)$, so that the dependence of $\hat{\boldsymbol{Y}}_{\rm d}$ on ω rephrases, for the considered physical situation, the explicit dependence of $\tilde{\boldsymbol{Y}}_{\rm d}$ on $\mathcal{X}$ and $\mathcal{T}$. Accordingly, (9) takes on the form of an ordinary differential equation for $\boldsymbol{K}$, controlled by ω, and influenced by the body's deformation through its dependence on $\boldsymbol{F}$, i.e.,

$$\hat{\boldsymbol{Y}}_{\rm d} \circ (\boldsymbol{F}, \boldsymbol{K}, \dot{\boldsymbol{K}}, \omega) + \hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K}) = \hat{\boldsymbol{Z}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \operatorname{Grad} \omega). \tag{17}$$

Note that one may also let $\hat{\boldsymbol{Y}}_{\rm d}$ depend on $\operatorname{Grad}\omega$, although this would lead, in general, to anisotropic constitutive laws for $\hat{\boldsymbol{Y}}_{\rm d}$, which we do not consider here. To motivate this statement, we remark that, in spite of the important role that the nutrients play in our model, their presence in the thermodynamic formulation of our present theory is marginal. Indeed, if we opted for a model capable of taking into account the nutrients in a thermodynamically consistent way, we should consider also the full set of balance laws associated with their dynamics. More specifically, to consistently recover Fick's law of diffusion, we should study this phenomenon in the dissipation inequality, which would call for including $\operatorname{Grad}\omega$ in the list of the independent constitutive variables of the theory [Hassanizadeh 1986; Bennethum et al. 2000; Grillo et al. 2012]. In this respect, assuming $\hat{\boldsymbol{Y}}_{\rm d}$ to depend also on $\operatorname{Grad}\omega$ would be equivalent to describe couplings between growth and nutrients' diffusion, which, to our knowledge, are not straightforward to detect. For these reasons, here, we neglect any dependence of $\hat{\boldsymbol{Y}}_{\rm d}$ on $\operatorname{Grad}\omega$.

The constitutive expression of $\boldsymbol{Y}_{\rm d}$ must comply with the dissipation inequality, which, after the identifications in (7a)–(7c) and (8) are made, can be written as (see, e.g., [DiCarlo and Quiligotti 2002; Olsson and Klarbring 2008; Crevacore et al. 2019; Grillo and Di Stefano 2023b; Licari 2021])

$$\mathcal{D}_{\rm R} = \boldsymbol{Y}_{\rm d} : \boldsymbol{K}^{-1}\dot{\boldsymbol{K}} = J_{\boldsymbol{K}} \boldsymbol{Y}_{\rm d\nu} : \boldsymbol{L}_{\boldsymbol{K}} \geq 0, \quad \boldsymbol{Y}_{\rm d} := \hat{\boldsymbol{Y}}_{\rm d} \circ (\boldsymbol{F}, \boldsymbol{K}, \dot{\boldsymbol{K}}, \omega), \tag{18}$$

where $\boldsymbol{Y}_{\rm d\nu} := J_{\boldsymbol{K}}^{-1} \boldsymbol{K}^{-\rm T} \boldsymbol{Y}_{\rm d} \boldsymbol{K}^{\rm T}$ and $\boldsymbol{L}_{\boldsymbol{K}} := \dot{\boldsymbol{K}} \boldsymbol{K}^{-1}$ are the counterparts of $\boldsymbol{Y}_{\rm d}$ and $\boldsymbol{K}^{-1}\dot{\boldsymbol{K}}$ associated with the body's natural state. By considering the transformation of the Eshelby stress tensor and of the external force $\boldsymbol{Z}$, i.e.,

$$\boldsymbol{H}_\nu := J_{\boldsymbol{K}}^{-1} \boldsymbol{K}^{-\rm T} [\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K})] \boldsymbol{K}^{\rm T} \quad \text{and} \quad \boldsymbol{Z}_\nu := J_{\boldsymbol{K}}^{-1} \boldsymbol{K}^{-\rm T} \boldsymbol{Z} \boldsymbol{K}^{\rm T},$$

with $\boldsymbol{Z}$ given in (10), (9) can be rewritten as

$$\boldsymbol{Y}_{\rm d\nu} + \boldsymbol{H}_\nu = \boldsymbol{Z}_\nu. \tag{19}$$

5.1. ***Additional constitutive restrictions.*** Equation (19) suggests to place four restrictions on the constitutive representation of $\boldsymbol{Y}_{\rm d\nu}$. Such restrictions were first put forward by [Epstein and Maugin 2000] in the context of growth in uniform bodies, but within a theoretical framework rather different from ours. Indeed, while the scope of [Epstein and Maugin 2000] was to find the most general form of admissible evolution laws for $\boldsymbol{K}$, ours is to determine admissible constitutive functions for $\boldsymbol{Y}_{\rm d}$.

Thus, our task is now to adapt those restrictions to our approach by rephrasing them appropriately.

We call the restrictions under study *"uniformity"*, *"frame indifference"*, *independence of the selected reference placement*, and, upon assuming isotropy, *covariance under the full group of* (*proper*) *rotations of the natural state*. We notice that the first three requirements adopt, with some changes, the terminology of [Epstein and Maugin 2000], and that, although frame indifference (objectivity) is one of the requirements of the general theory of constitutive laws, it is discussed here in order to adhere to their presentation.

Uniformity. In their model of growth in *"uniform bodies"*, [Epstein and Maugin 2000] require the *"evolution law"* for $\boldsymbol{K}$ to comply with the property of *"uniformity"*. One of the aspects of this property is that, if the model parameters do not depend explicitly on material points and time, and if other sources of inhomogeneity, such as the mass fraction of the nutrients, are disregarded, it must be possible to formulate the evolution law for $\boldsymbol{K}$ in such a way that the inhomogeneity of the body be resolved through the dependence of the evolution law on $\boldsymbol{K}$ itself. In other words, $\boldsymbol{K}$ "absorbs" the body's *"material inhomogeneities"* [Epstein and Maugin 2000]. In our framework, instead, this concept must be rephrased in terms of constitutive laws for $\boldsymbol{Y}_{\mathrm{d}}$, and, since we consider the presence of chemical agents, we require that, if the model parameters are independent on material points and time, $\hat{\boldsymbol{Y}}_{\mathrm{d}}$ must be such that $\boldsymbol{Y}_{\mathrm{d}} = \hat{\boldsymbol{Y}}_{\mathrm{d}} \circ (\boldsymbol{F}, \boldsymbol{K}, \dot{\boldsymbol{K}}, \omega)$, thereby "absorbing" the body's material inhomogeneities through $\boldsymbol{K}$ and ω. This result, in fact, brings us back to the constitutive form of $\boldsymbol{Y}_{\mathrm{d}}$ given in (17). Before going further, we emphasize that our growth tensor $\boldsymbol{K}$ corresponds to the inverse of the tensor field termed *"transplant operator"* by [Epstein and Maugin 2000].

Frame indifference (objectivity). Equation (19) must be unaffected by the superposition of rigid motions to the motion of the body. Accordingly, it must remain unchanged if $\boldsymbol{F}$ is transformed into $\tilde{\boldsymbol{F}} = \mathbf{q}\boldsymbol{F}$, with $\mathbf{q}$ being any spatial proper orthogonal tensor. To ensure this, the constitutive expression of each term of (19) should depend on $\boldsymbol{F}$ through the Cauchy–Green deformation tensor $\boldsymbol{C}$. Whereas this property is automatically satisfied by the definition of $\hat{\boldsymbol{Z}}$ in (10) and (15), and by the constitutive representation of $\boldsymbol{H}_{\nu}$, which can be proven to depend exclusively on $\boldsymbol{C}_{\mathrm{e}}$, we must assume that

$$\boldsymbol{Y}_{\mathrm{d}\nu} = \hat{\boldsymbol{Y}}_{\mathrm{d}\nu} \circ (\boldsymbol{F}, \boldsymbol{K}, \dot{\boldsymbol{K}}, \omega) \equiv \overline{\boldsymbol{Y}}_{\mathrm{d}\nu} \circ (\boldsymbol{C}, \boldsymbol{K}, \dot{\boldsymbol{K}}, \omega). \tag{20}$$

Independence of the selected reference placement. Since $\boldsymbol{H}_{\nu}$ and $\boldsymbol{Z}_{\nu}$ do not vary under changes of the reference placement of the body, nor do their constitutive representations, $\boldsymbol{Y}_{\mathrm{d}\nu}$ should also be invariant under the same class of transformations. Thus, (19) as a whole, being associated with the natural state of the body, should be unaffected by such transformations. To describe this property, we first consider a placement $\tilde{\mathscr{B}} \neq \mathscr{B}$, the time-independent diffeomorphism $\xi : \tilde{\mathscr{B}} \to \mathscr{B}$, such that each $\tilde{X} \in \tilde{\mathscr{B}}$ is univocally remapped into $X = \xi(\tilde{X}) \in \mathscr{B}$, and the Jacobian tensor $\Xi(\tilde{X}) := D\xi(\tilde{X}) : T_{\tilde{X}}\tilde{\mathscr{B}} \to T_X\mathscr{B}$, with $\det \Xi(\tilde{X}) > 0$, for all $\tilde{X} \in \tilde{\mathscr{B}}$. Then, the transformed tensors $\tilde{\boldsymbol{F}}(\tilde{X}, t) : T_{\tilde{X}}\tilde{\mathscr{B}} \to T_x\mathscr{S}$, $\tilde{\boldsymbol{C}}(\tilde{X}, t) : T_{\tilde{X}}\tilde{\mathscr{B}} \to T_{\tilde{X}}{}^*\tilde{\mathscr{B}}$, and $\tilde{\boldsymbol{K}}(\tilde{X}, t) : T_{\tilde{X}}\tilde{\mathscr{B}} \to \mathscr{N}_{\xi(\tilde{X})}(t)$ are related to $\boldsymbol{F}(X, t)$, $\boldsymbol{C}(X, t)$, and $\boldsymbol{K}(X, t)$ through $\tilde{\boldsymbol{F}}(\tilde{X}, t) = \boldsymbol{F}(\xi(\tilde{X}), t)\Xi(\tilde{X})$, $\tilde{\boldsymbol{C}}(\tilde{X}, t) = \Xi^{\mathrm{T}}(\xi(\tilde{X}))\boldsymbol{C}(\xi(\tilde{X}), t)\Xi(\tilde{X})$, and $\tilde{\boldsymbol{K}}(\tilde{X}, t) = \boldsymbol{K}(\xi(\tilde{X}), t)\Xi(\tilde{X})$. With these premises, we require

$$\bar{\boldsymbol{Y}}_{\mathrm{d}\nu}\big(\boldsymbol{C}(X, t), \boldsymbol{K}(X, t), \dot{\boldsymbol{K}}(X, t), \omega(X, t)\big) = \bar{\boldsymbol{Y}}_{\mathrm{d}\nu}\big(\Xi^{\mathrm{T}}(X)\boldsymbol{C}(X, t)\Xi(\xi^{-1}(X)), \boldsymbol{K}(X, t)\Xi(\xi^{-1}(X)), \dot{\boldsymbol{K}}(X, t)\Xi(\xi^{-1}(X)), \omega(X, t)\big). \quad (21)$$

To fulfill (21), we postulate that the constitutive function of $\boldsymbol{Y}_{\mathrm{d}\nu}$ depends on $\boldsymbol{C}$ and $\boldsymbol{K}$ through $\boldsymbol{C}_{\mathrm{e}} = \boldsymbol{K}^{-\mathrm{T}}\boldsymbol{C}\boldsymbol{K}^{-1}$, and on $\boldsymbol{K}$ and $\dot{\boldsymbol{K}}$ through $\boldsymbol{L}_{\boldsymbol{K}} = \dot{\boldsymbol{K}}\boldsymbol{K}^{-1}$, i.e.,

$$\boldsymbol{Y}_{\mathrm{d}\nu} = \bar{\boldsymbol{Y}}_{\mathrm{d}\nu} \circ (\boldsymbol{C}, \boldsymbol{K}, \dot{\boldsymbol{K}}, \omega) = \check{\boldsymbol{Y}}_{\mathrm{d}\nu} \circ (\boldsymbol{C}_{\mathrm{e}}, \boldsymbol{L}_{\boldsymbol{K}}, \omega). \quad (22)$$

In obtaining (21) and (22), we have reelaborated a procedure that [Epstein and Maugin 2000] had previously developed to show that, in order for an evolution law for the transplant operator to be admissible, the evolution law itself should be invariant under changes of the *"reference configuration"*. In doing this, we have also adapted the original procedure of [Epstein and Maugin 2000] to our framework. In addition, we remark that this procedure has also been reviewed by [Epstein and Elżanowski 2007], where it is formulated by introducing the concept of *"archetype"* of the material.

Covariance under (proper) rotations of the natural state. Before discussing this restriction, we emphasize that [Epstein and Maugin 2000] requires its evolution law for $\boldsymbol{K}$ to be invariant under transformations *"of the crystal of reference"* that reflect the possible material symmetries of the medium under study. To formalize this restriction in our context, we require from here on that the body under study is *isotropic*, and we consider the covariance of the constitutive expression of $\boldsymbol{Y}_{\mathrm{d}\nu}$ under the full group of the proper rotations of the body's natural state. Hence, let $\boldsymbol{\Omega}(X)$ be a proper orthogonal tensor that generates a "rotated" copy of the considered natural state at $X \in \mathscr{B}$ and $t \in \mathscr{I}$, and such that $\boldsymbol{K}(X, t)$ is transformed into $\tilde{\boldsymbol{K}}(X, t) = \boldsymbol{\Omega}(X)\boldsymbol{K}(X, t)$. Then, $\boldsymbol{C}_{\mathrm{e}}$ and $\boldsymbol{L}_{\boldsymbol{K}}$ transform into

$$\tilde{\boldsymbol{C}}_{\mathrm{e}}(X, t) = \boldsymbol{\Omega}^{-\mathrm{T}}(X)\boldsymbol{C}_{\mathrm{e}}(X, t)\boldsymbol{\Omega}^{-1}(X), \quad \tilde{\boldsymbol{L}}_{\boldsymbol{K}}(X, t) = \boldsymbol{\Omega}(X)\boldsymbol{L}_{\boldsymbol{K}}(X, t)\boldsymbol{\Omega}^{-1}(X), \quad (23)$$

and the constitutive relation (22) is *covariant under proper rotations of the natural state* if, and only if, it holds true that (see also [Licari 2021])

$$\check{\boldsymbol{Y}}_{\mathrm{d}\nu}(\tilde{\boldsymbol{C}}_{\mathrm{e}}(X, t), \tilde{\boldsymbol{L}}_{\boldsymbol{K}}(X, t), \omega(X, t)) = \boldsymbol{\Omega}^{-\mathrm{T}}(X)\{\check{\boldsymbol{Y}}_{\mathrm{d}\nu}(\boldsymbol{C}_{\mathrm{e}}(X, t), \boldsymbol{L}_{\boldsymbol{K}}(X, t), \omega(X, t)\}\boldsymbol{\Omega}^{\mathrm{T}}(X). \quad (24)$$

5.2. ***Final form of the constitutive law for Y_d.*** To meet the restrictions discussed above, it is convenient to rewrite (18) as [Grillo et al. 2012; Licari 2021]

$$\mathcal{D}_R = J_K C_e^{-1} Y_{d\nu} : C_e L_K \geq 0. \tag{25}$$

Using (25) has the advantage that $C_e^{-1} Y_{d\nu}$ helps exploit possible symmetry properties of $Y_{d\nu}$. This is the case, for instance, when Z vanishes identically and, thus, it holds that $Y_{d\nu} = -H_\nu$. Indeed, since H_ν complies by its own definition with the condition $C_e^{-1} H_\nu = H_\nu^T C_e^{-1}$, also $Y_{d\nu}$ must be such that $C_e^{-1} Y_{d\nu}$ is symmetric (see, e.g., [Maugin and Epstein 1998; Grillo et al. 2012]).

For simplicity, we prescribe $C_e^{-1} Y_{d\nu}$ to be constitutively represented by a linear, tensor-valued function of $C_e L_K$. Hence, by virtue of the constitutive form of $Y_{d\nu}$ reported in (22), and using the notation of [Federico 2012] and the approach of [Grillo et al. 2012], we write

$$\begin{aligned} &C_e^{-1} Y_{d\nu} \equiv C_e^{-1}[\check{Y}_{d\nu} \circ (C_e, L_K, \omega)] = [\hat{\mathbb{T}}_\nu^\sharp \circ (C_e, \omega)] : C_e L_K \\ &\Rightarrow \; Y_{d\nu} \equiv \check{Y}_{d\nu} \circ (C_e, L_K, \omega) = C_e\big\{[\hat{\mathbb{T}}_\nu^\sharp \circ (C_e, \omega)] : C_e L_K\big\}, \end{aligned} \tag{26}$$

where $\hat{\mathbb{T}}_\nu^\sharp \circ (C_e, \omega)$ is a fourth-order tensor-valued function decomposed as

$$\hat{\mathbb{T}}_\nu^\sharp \circ (C_e, \omega) := [\hat{\mathfrak{a}}_\nu \circ \omega]\,[\hat{\mathbb{V}}_\nu^\sharp \circ C_e] + 2\,[\hat{\mathfrak{b}}_\nu \circ \omega]\,[\hat{\mathbb{S}}_\nu^\sharp \circ C_e] + 2\,[\hat{\mathfrak{c}}_\nu \circ \omega]\,[\hat{\mathbb{A}}_\nu^\sharp \circ C_e] \tag{27}$$

[Pericak-Spector and Spector 1995; Grillo and Wittum 2010; Grillo et al. 2019a; Licari 2021]. In (27), $\hat{\mathfrak{a}}_\nu$, $\hat{\mathfrak{b}}_\nu$, and $\hat{\mathfrak{c}}_\nu$ are real-valued functions that have the meaning of "generalized viscosities", and satisfy the thermodynamic restrictions

$$[\hat{\mathfrak{a}}_\nu \circ \omega] + 2\,[\hat{\mathfrak{b}}_\nu \circ \omega] \geq 0, \quad \hat{\mathfrak{b}}_\nu \circ \omega \geq 0, \quad \hat{\mathfrak{c}}_\nu \circ \omega \geq 0. \tag{28}$$

Also, $\hat{\mathbb{V}}_\nu^\sharp \circ C_e$, $\hat{\mathbb{S}}_\nu^\sharp \circ C_e$, and $\hat{\mathbb{A}}_\nu^\sharp \circ C_e$ are fourth-order tensor functions defined by

$$\hat{\mathbb{V}}_\nu^\sharp \circ C_e := \tfrac{1}{3} C_e^{-1} \otimes C_e^{-1}, \tag{29a}$$

$$\hat{\mathbb{S}}_\nu^\sharp \circ C_e := \tfrac{1}{2}[C_e^{-1} \underline{\otimes} C_e^{-1} + C_e^{-1} \overline{\otimes} C_e^{-1}], \tag{29b}$$

$$\hat{\mathbb{A}}_\nu^\sharp \circ C_e := \tfrac{1}{2}[C_e^{-1} \underline{\otimes} C_e^{-1} - C_e^{-1} \overline{\otimes} C_e^{-1}], \tag{29c}$$

and such that their double-contraction with any "fully covariant" second-order tensor T_ν, associated with the body's natural state, extracts the spherical, symmetric, and skew-symmetric parts of T_ν induced by C_e^{-1}, i.e.,

$$[\hat{\mathbb{V}}_\nu^\sharp \circ C_e] : T_\nu = \tfrac{1}{3}\,\mathrm{tr}[C_e^{-1} T_\nu] C_e^{-1} = \tfrac{1}{3}\,\mathrm{tr}[(C_e^{-1} T_\nu C_e^{-1}) C_e] C_e^{-1}, \tag{30a}$$

$$[\hat{\mathbb{S}}_\nu^\sharp \circ C_e] : T_\nu = C_e^{-1}(\mathrm{sym}\, T_\nu) C_e^{-1} = \mathrm{sym}(C_e^{-1} T_\nu C_e^{-1}), \tag{30b}$$

$$[\hat{\mathbb{A}}_\nu^\sharp \circ C_e] : T_\nu = C_e^{-1}(\mathrm{skew}\, T_\nu) C_e^{-1} = \mathrm{skew}(C_e^{-1} T_\nu C_e^{-1}). \tag{30c}$$

Finally, the results achieved in (26), (27), and (30a)–(30c) yield (see also [Grillo and Di Stefano 2023b; Licari 2021])

$$\begin{aligned}
&\hat{\boldsymbol{Y}}_{\mathrm{d}} \circ (\boldsymbol{F}, \boldsymbol{K}, \dot{\boldsymbol{K}}, \omega) \\
&\quad = J_{\boldsymbol{K}} \boldsymbol{K}^{\mathrm{T}} \big(\boldsymbol{C}_{\mathrm{e}} \big\{ [\hat{\mathbb{T}}_{\nu}^{\sharp} \circ (\boldsymbol{C}_{\mathrm{e}}, \omega)] : \boldsymbol{C}_{\mathrm{e}} \boldsymbol{L}_{\boldsymbol{K}} \big\} \big) \boldsymbol{K}^{-\mathrm{T}} \\
&\quad = \tfrac{1}{3} J_{\boldsymbol{K}} [\hat{\mathfrak{a}}_{\nu} \circ \omega] \operatorname{tr}(\boldsymbol{K}^{-1} \dot{\boldsymbol{K}}) \boldsymbol{I}^{\mathrm{T}} \\
&\qquad + 2 J_{\boldsymbol{K}} [\hat{\mathfrak{b}}_{\nu} \circ \omega] \boldsymbol{C} \operatorname{sym}[(\boldsymbol{K}^{-1} \dot{\boldsymbol{K}}) \boldsymbol{C}^{-1}] + 2 J_{\boldsymbol{K}} [\hat{\mathfrak{c}}_{\nu} \circ \omega] \boldsymbol{C} \operatorname{skew}[(\boldsymbol{K}^{-1} \dot{\boldsymbol{K}}) \boldsymbol{C}^{-1}] \\
&\quad = [\hat{\mathbb{T}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)] : (\boldsymbol{K}^{-1} \dot{\boldsymbol{K}}),
\end{aligned} \tag{31}$$

where the function $\hat{\mathbb{T}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)$, valued in the space of fourth-order tensors, is given by

$$\begin{aligned}
\hat{\mathbb{T}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega) := \tfrac{1}{3} J_{\boldsymbol{K}} [\hat{\mathfrak{a}}_{\nu} \circ \omega] \boldsymbol{I}^{\mathrm{T}} \otimes \boldsymbol{I}^{\mathrm{T}} + J_{\boldsymbol{K}} [\hat{\mathfrak{b}}_{\nu} \circ \omega] \{ \boldsymbol{C} \underline{\otimes} \boldsymbol{C}^{-1} + \boldsymbol{I}^{\mathrm{T}} \overline{\otimes} \boldsymbol{I} \} \\
+ J_{\boldsymbol{K}} [\hat{\mathfrak{c}}_{\nu} \circ \omega] \{ \boldsymbol{C} \underline{\otimes} \boldsymbol{C}^{-1} - \boldsymbol{I}^{\mathrm{T}} \overline{\otimes} \boldsymbol{I} \}.
\end{aligned} \tag{32}$$

By virtue of (10) and (32), the force balance (9) can be rewritten as

$$[\hat{\mathbb{T}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)] : (\boldsymbol{K}^{-1} \dot{\boldsymbol{K}}) = -\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K}) + \hat{\boldsymbol{Z}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \operatorname{Grad} \omega). \tag{33}$$

Equation (33) describes the evolution of $\boldsymbol{K}$, and should be solved in conjunction with (4a)–(4c), along with suitable initial conditions for $\boldsymbol{K}$ and χ.

Remark 1 (the generalized viscosity function $\hat{\mathfrak{c}}_{\nu} \circ \omega \geq 0$). By left multiplying (33) by $\boldsymbol{C}^{-1}$, and using (31), (33) admits the equivalent formulation

$$\begin{aligned}
&\tfrac{1}{3} J_{\boldsymbol{K}} [\hat{\mathfrak{a}}_{\nu} \circ \omega] \operatorname{tr}(\boldsymbol{K}^{-1} \dot{\boldsymbol{K}}) \boldsymbol{C}^{-1} \\
&\quad + 2 J_{\boldsymbol{K}} [\hat{\mathfrak{b}}_{\nu} \circ \omega] \operatorname{sym}[(\boldsymbol{K}^{-1} \dot{\boldsymbol{K}}) \boldsymbol{C}^{-1}] + 2 J_{\boldsymbol{K}} [\hat{\mathfrak{c}}_{\nu} \circ \omega] \operatorname{skew}[(\boldsymbol{K}^{-1} \dot{\boldsymbol{K}}) \boldsymbol{C}^{-1}] \\
&\qquad = -\boldsymbol{C}^{-1} [\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K})] + \boldsymbol{C}^{-1} [\hat{\boldsymbol{Z}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \operatorname{Grad} \omega)].
\end{aligned} \tag{34}$$

The first term on the right-hand side of (34) is symmetric by virtue of the properties of the Eshelby stress tensor (see (8)), while the second term is symmetric as a consequence of the definition of $\hat{\boldsymbol{Z}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \operatorname{Grad} \omega)$ provided in (10) and (15). Therefore, the whole right-hand side of (34) is symmetric and, thus, so has to be its left-hand side, too. Hence, (33) splits into the system of equations

$$[\hat{\mathbb{T}}_{\mathrm{s}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)] : (\boldsymbol{K}^{-1} \dot{\boldsymbol{K}}) = -\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K}) + \hat{\boldsymbol{Z}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \operatorname{Grad} \omega), \tag{35a}$$

$$2 J_{\boldsymbol{K}} [\hat{\mathfrak{c}}_{\nu} \circ \omega] \operatorname{skew}[(\boldsymbol{K}^{-1} \dot{\boldsymbol{K}}) \boldsymbol{C}^{-1}] = \boldsymbol{0}, \tag{35b}$$

where $\hat{\mathbb{T}}_{\mathrm{s}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)$ is defined by the sum of the first two terms of (32).

6. The a posteriori growth law

By putting together all the results obtained so far, and setting $T :=]t_{\text{in}}, t_{\text{fin}}]$, the equations to be solved within the a posteriori approach considered in this work are given by

$$\mathrm{Div}[\hat{\boldsymbol{P}} \circ (\boldsymbol{F}, \boldsymbol{K})] = \boldsymbol{0}, \qquad \mathscr{B} \times T, \tag{36a}$$

$$\chi = \chi_{\mathrm{b}}, \qquad \partial_{\mathrm{D}}^{\chi}\mathscr{B} \times T, \tag{36b}$$

$$[\hat{\boldsymbol{P}} \circ (\boldsymbol{F}, \boldsymbol{K})]\boldsymbol{N} = \boldsymbol{\tau}, \qquad \partial_{\mathrm{N}}^{\chi}\mathscr{B} \times T, \tag{36c}$$

$$[\hat{\mathbb{T}}_{\mathrm{s}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)] : (\boldsymbol{K}^{-1}\dot{\boldsymbol{K}}) = -\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K}) + \hat{\boldsymbol{Z}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \mathrm{Grad}\,\omega), \qquad \mathscr{B} \times T, \tag{36d}$$

$$2J_{\boldsymbol{K}}[\hat{\mathfrak{c}}_{\nu} \circ \omega]\,\mathrm{skew}[(\boldsymbol{K}^{-1}\dot{\boldsymbol{K}})\boldsymbol{C}^{-1}] = \boldsymbol{0}, \qquad \mathscr{B} \times T, \tag{36e}$$

$$\boldsymbol{K}(X, t_{\text{in}}) = \boldsymbol{K}_{\text{in}}(X), \qquad \mathscr{B}. \tag{36f}$$

The system (36a)–(36f) must be solved together with a diffusion-reaction equation for the nutrients. This has been recently done by [Grillo and Di Stefano 2023a], while some preliminary simulations were performed by [Licari 2021]. Here, instead, we give prominence to two remarks:

Remark 2 (determination of the a posteriori growth law). By taking the trace of (35a), or (36d), recalling the identification $R_{\gamma} \equiv \mathrm{tr}(\boldsymbol{K}^{-1}\dot{\boldsymbol{K}})$ and the definition (10), and hypothesizing $[\hat{\mathfrak{a}}_{\nu} \circ \omega] + 2\,[\hat{\mathfrak{b}}_{\nu} \circ \omega] > 0$, we obtain

$$R_{\gamma} \equiv \mathrm{tr}(\boldsymbol{K}^{-1}\dot{\boldsymbol{K}}) = \frac{-\mathrm{tr}[\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K})]}{J_{\boldsymbol{K}}\{[\hat{\mathfrak{a}}_{\nu} \circ \omega] + 2\,[\hat{\mathfrak{b}}_{\nu} \circ \omega]\}} + \frac{\hat{\Gamma} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)}{[\hat{\mathfrak{a}}_{\nu} \circ \omega] + 2\,[\hat{\mathfrak{b}}_{\nu} \circ \omega]} + \frac{Q_{\nu\ell} + 2Q_{\nu\mathrm{t}}}{[\hat{\mathfrak{a}}_{\nu} \circ \omega] + 2\,[\hat{\mathfrak{b}}_{\nu} \circ \omega]}\|\mathrm{Grad}\,\omega\|_{\boldsymbol{C}^{-1}}. \tag{37}$$

Thus, at variance with [Licari 2021], in which only the first two summands on the far right-hand side appear (and the second one is defined differently from ours), in the considered a posteriori approach, the growth law is the sum of three terms:

- The first one, which involves the Eshelby stress tensor, is of purely mechanical origin, and shows how, within the theoretical approach adopted in our work, the mechanics of the body exerts a direct influence on the body's mass variation.
- The second term features the factor $\hat{\Gamma} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)$, as defined in (11), (12a) and (12b), and mimics the phenomenological law specified in (14) with the purpose of making our model as close as possible to the phenomenology reported by [Mascheroni et al. 2016]. In particular, if the generalized viscosities are assumed to be constant, so that we can set $\hat{\mathfrak{a}}_{\nu} \circ \omega \equiv a_{\nu}$, $\hat{\mathfrak{b}}_{\nu} \circ \omega \equiv b_{\nu}$, and $\hat{\mathfrak{c}}_{\nu} \circ \omega \equiv c_{\nu}$, with a_{ν},

b_ν and c_ν such that $a_\nu + 2b_\nu > 0$, $b_\nu > 0$, and $c_\nu > 0$, the second summand on the right-hand side of (37) becomes

$$\frac{\hat{\Gamma} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)}{a_\nu + 2b_\nu} = \frac{\kappa_{\rm a}}{a_\nu + 2b_\nu}[\hat{\Gamma}_{\rm a} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)] + \frac{\kappa_{\rm r}}{a_\nu + 2b_\nu}[\hat{\Gamma}_{\rm r} \circ \omega], \tag{38}$$

and the factors $\kappa_{\rm a}/[a_\nu + 2b_\nu]$ and $\kappa_{\rm r}/[a_\nu + 2b_\nu]$ have the physical dimensions of the inverse of a characteristic time. Hence, they play the same role as the constant coefficients $\zeta_{\rm a}$ and $\zeta_{\rm r}$ in the phenomenological growth law in (14). In fact, for given values of a_ν, b_ν, $\zeta_{\rm a}$, and $\zeta_{\rm r}$, one may estimate $\kappa_{\rm a}$ and $\kappa_{\rm r}$ as

$$\kappa_{\rm a} = [a_\nu + 2b_\nu]\zeta_{\rm a} > 0 \quad \text{and} \quad \kappa_{\rm r} = -[a_\nu + 2b_\nu]\zeta_{\rm r} < 0. \tag{39}$$

• The third term measures the contribution of the gradient of the nutrients' mass fraction on the growth law and, in our model, it is modulated by the ratio between the "bulk dispersivity" $[Q_{\nu\ell} + 2Q_{\nu{\rm t}}]$ and the bulk viscosity $[a_\nu + 2b_\nu]$, i.e.,

$$\frac{Q_{\nu\ell} + 2Q_{\nu{\rm t}}}{a_\nu + 2b_\nu}. \tag{40}$$

• By comparing $R_{\gamma({\rm ph})}$ with (10)–(13), which define $\boldsymbol{Z}$, we notice that we have constructed the force $\boldsymbol{Z}$ in such a way that the growth law computed a posteriori as in (37) portrays the phenomenology captured by $R_{\gamma({\rm ph})}$, and extends it by including some chemo-mechanical effects foreseen by the theory.

Remark 3 (the sign of R_γ or its vanishing). Within the a posteriori approach developed in our work, the sign of R_γ, or its vanishing, is the result of the combination of the volumetric parts of the generalized forces contributing to the force balance (35a), dual to $\boldsymbol{K}^{-1}\dot{\boldsymbol{K}}$, as shown in (37). Therefore, it cannot be decided a priori whether R_γ is positive (mass accretion), negative (mass resorption), or null. More importantly, none of these behaviors can be ascribed exclusively to the value of the nutrients' mass fraction, regardless of the presence of the activation factors $\langle h_{\rm a} \circ \omega \rangle_+$ and $\langle h_{\rm r} \circ \omega \rangle_+$ in the definition of $\hat{\Gamma} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)$ given in (10). This is essentially due to the fact that, within the a posteriori approach, growth *is not* a direct consequence of the availability of the nutrients. In other words, although the role of the nutrients is fundamental, as testified by the term $[\hat{\Gamma} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega)]/(a_\nu + 2b_\nu)$ in (37) and (38), it is not more important than the role of the other summands of (37), at least in principle. This is because, in the vision of the a posteriori approach, growth, represented by ${\rm tr}(\boldsymbol{K}^{-1}\dot{\boldsymbol{K}})$, is the volumetric expression of the *kinematics necessary to fulfill the force balance* (33), or (35a). In turn, such force balance presents, on its right-hand side, both a purely mechanical force, i.e., the Eshelby stress tensor, and the nonconventional force that translates chemical interactions into mechanical ones, i.e., $\hat{\boldsymbol{Z}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, {\rm Grad}\,\omega)$ [DiCarlo 2005; Grillo and Di Stefano 2023b]. Indeed, within the a posteriori approach, in addition to the variation of mass that stems from the availability, or nonavailability, of the nutrients, there is room also for the variation of mass, dual to $-\mathrm{tr}[\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K})]$, that depends on the evolution of *"material inhomogeneities"*, as predicted by [Epstein and Maugin 2000], and now framed in the context put forward by [DiCarlo and Quiligotti 2002]. It is the balance of all these mass variations that yields the sign of R_γ or its vanishing. Finally, we notice that the influence of $\mathrm{tr}[\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K})]$, i.e., of the configurational mechanical stress, on R_γ cannot be eliminated in the present model. Indeed, even though we set $\alpha = 0$ in the definition of $\hat{\Gamma}_\mathrm{a}$ (thereby suppressing the dependence on $\langle \hat{\wp} \circ (\boldsymbol{F}, \boldsymbol{K}) \rangle_+$ and, thus, dispensing the effect of mechanotransduction), we would still have to consider $\mathrm{tr}[\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K})]$ as one of the driving forces for R_γ.

Remark 4 ("Cauchy's gauge" and growth law). The concept of *"Cauchy's gauge"* was introduced in the book [Epstein and Elżanowski 2007, pp. 112–116, Sections 5.1–5.4], according to which the constitutive expression of the Cauchy stress tensor of a hyperelastic medium remains invariant under the gauge transformation $\hat{\Psi}_\mathrm{R} \mapsto \tilde{\Psi}_\mathrm{R} = \hat{\Psi}_\mathrm{R} + \hat{\Psi}_{\mathrm{R}0}$, where $\hat{\Psi}_\mathrm{R}$ is the Helmholtz free energy density of the considered model (which we might call "representative" of the class of equivalence of the energy densities yielding the same Cauchy stress tensor), and $\hat{\Psi}_{\mathrm{R}0}$ is an energy density independent of $\boldsymbol{F}$ that can be selected with a certain freedom. Epstein and Elżanowski [2007] also recall that, since the gauge transformation reported above is performed with respect to quantities associated with the medium's reference placement, the Eshelby stress tensor generated by $\tilde{\Psi}_\mathrm{R}$ differs from the one generated by $\hat{\Psi}_\mathrm{R}$, i.e., $\boldsymbol{H}$, by a term that is hydrostatic as long as $\hat{\Psi}_{\mathrm{R}0}$ is constant. More generally, however, and more consistently with the theory presented in our work (Epstein and Elżanowski [2007] address the case of material uniformity), the invariance of the Cauchy stress tensor is preserved also if the transformation of the Helmholtz free energy density is carried out as

$$\hat{\Psi}_\mathrm{R} \circ (\boldsymbol{F}, \boldsymbol{K}) \mapsto \tilde{\Psi}_\mathrm{R} \circ (\boldsymbol{F}, \boldsymbol{K}) = \hat{\Psi}_\mathrm{R} \circ (\boldsymbol{F}, \boldsymbol{K}) + \hat{\Psi}_{\mathrm{R}0} \circ \boldsymbol{K}, \tag{41}$$

where $\hat{\Psi}_\mathrm{R} \circ (\boldsymbol{F}, \boldsymbol{K})$ is given in (7a), and $\hat{\Psi}_{\mathrm{R}0} \circ \boldsymbol{K} := J_{\boldsymbol{K}} [\hat{\Psi}_{\nu 0} \circ \boldsymbol{K}]$ is any energy density depending solely on $\boldsymbol{K}$, and obtained by pulling back the energy density $\hat{\Psi}_{\nu 0} \circ \boldsymbol{K}$, written per unit volume of the natural state, to the reference placement. Equation (41) implies that, although the Cauchy stress tensor remains unchanged, the Eshelby stress tensor transforms as

$$\begin{aligned} \boldsymbol{H} \mapsto \tilde{\boldsymbol{H}} = \boldsymbol{K}^\mathrm{T} \left[\frac{\partial \tilde{\Psi}_\mathrm{R}}{\partial \boldsymbol{K}} \circ (\boldsymbol{F}, \boldsymbol{K}) \right] &= \underbrace{\boldsymbol{K}^\mathrm{T} \left[\frac{\partial \hat{\Psi}_\mathrm{R}}{\partial \boldsymbol{K}} \circ (\boldsymbol{F}, \boldsymbol{K}) \right]}_{\equiv \boldsymbol{H}} + \underbrace{\boldsymbol{K}^\mathrm{T} \left[\frac{\partial \hat{\Psi}_{\mathrm{R}0}}{\partial \boldsymbol{K}} \circ \boldsymbol{K} \right]}_{=: \boldsymbol{H}_0} \\ &= \boldsymbol{H} + \boldsymbol{H}_0, \end{aligned} \tag{42}$$

with $\boldsymbol{H}_0$ being hydrostatic if the condition $\partial_{\boldsymbol{K}}\hat{\Psi}_{\nu 0}\circ\boldsymbol{K}=\boldsymbol{0}$ is identically satisfied for all $\boldsymbol{K}$, i.e., if $\hat{\Psi}_{\nu 0}$ is the constant function, or if $\hat{\Psi}_{\nu 0}\circ\boldsymbol{K}$ depends on $\boldsymbol{K}$ through $J_{\boldsymbol{K}}=\det\boldsymbol{K}$, only.

Within our theory, if the Helmholtz free energy density of the material is transformed as shown in (41), with $\hat{\Psi}_{\mathrm{R}0}\circ\boldsymbol{K}$ describing some interaction associated with $\boldsymbol{K}$, then the Eshelby stress tensor acquires the form given in (42), and the dynamic equation for $\boldsymbol{K}$, that is, (9), becomes

$$\boldsymbol{Y}_{\mathrm{d}}+(\boldsymbol{H}_0+\boldsymbol{H})=\boldsymbol{Z}, \tag{43}$$

where $\boldsymbol{Z}$ is given by (10). Conventionally, one can redefine the external force $\boldsymbol{Z}$ as $\boldsymbol{Z}_{\mathrm{new}}:=-\boldsymbol{H}_0+\boldsymbol{Z}$, and rewrite (43) as

$$\boldsymbol{Y}_{\mathrm{d}}+\boldsymbol{H}=\boldsymbol{Z}_{\mathrm{new}}, \tag{44}$$

so that R_γ takes on the definition

$$\begin{aligned} R_\gamma &\equiv \operatorname{tr}(\boldsymbol{K}^{-1}\dot{\boldsymbol{K}}) \\ &= \frac{-\operatorname{tr}\boldsymbol{H}_0-\operatorname{tr}[\hat{\boldsymbol{H}}\circ(\boldsymbol{F},\boldsymbol{K})]}{J_{\boldsymbol{K}}\{[\hat{\mathfrak{a}}_\nu\circ\omega]+2[\hat{\mathfrak{b}}_\nu\circ\omega]\}}+\frac{\hat{\Gamma}\circ(\boldsymbol{F},\boldsymbol{K},\omega)}{[\hat{\mathfrak{a}}_\nu\circ\omega]+2[\hat{\mathfrak{b}}_\nu\circ\omega]}+\frac{Q_{\nu\ell}+2Q_{\nu\mathrm{t}}}{[\hat{\mathfrak{a}}_\nu\circ\omega]+2[\hat{\mathfrak{b}}_\nu\circ\omega]}\|\operatorname{Grad}\omega\|_{\boldsymbol{C}^{-1}}. \end{aligned} \tag{45}$$

In fact, the property of the Eshelby stress tensor of not being invariant under the gauge transformation specified in (41) is consistent with the way in which R_γ is determined. Indeed, the addition of energy terms like $\hat{\Psi}_{\mathrm{R}0}\circ\boldsymbol{K}$ to the "representative" Helmholtz free energy density of the model, i.e., $\hat{\Psi}_{\mathrm{R}}\circ(\boldsymbol{F},\boldsymbol{K})$, indicates the activation of interactions that are *"configurational"* (in the jargon of [Gurtin 1995]) and, thus, that are naturally reflected by additional terms arising in the growth law.

On the other hand, a result similar to (45) is obtained also in those cases in which $\boldsymbol{Z}$ features a contribution that can be identified by differentiating with respect to $\boldsymbol{K}$ a potential density function of the same type (up to the sign) as $\hat{\Psi}_{\mathrm{R}0}$ of (41). This, indeed, amounts to redefining the Helmholtz free energy density of the material, without changing its Cauchy stress tensor. In other words, if $\boldsymbol{Z}$ can be written as

$$\boldsymbol{Z}=-\boldsymbol{H}_0+\boldsymbol{Z}_{\mathrm{old}}, \tag{46}$$

where $\boldsymbol{Z}_{\mathrm{old}}$ is provided by the right-hand side of (10), and $\boldsymbol{H}_0$ is now regarded as a second-order tensor field integrable with respect to $\boldsymbol{K}$, that is, a tensor field for which there exists a scalar-valued potential density function $\mathcal{U}_{\mathrm{R}}:=\hat{\mathcal{U}}_{\mathrm{R}}\circ(\boldsymbol{F},\boldsymbol{K})$ such that

$$-\boldsymbol{H}_0=\boldsymbol{K}^{\mathrm{T}}\Big[\frac{\partial\hat{\mathcal{U}}_{\mathrm{R}}}{\partial\boldsymbol{K}}\circ(\boldsymbol{F},\boldsymbol{K})\Big],\qquad \frac{\partial\hat{\mathcal{U}}_{\mathrm{R}}}{\partial\boldsymbol{F}}\circ(\boldsymbol{F},\boldsymbol{K})=\boldsymbol{0}, \tag{47}$$

then (9) becomes

$$\begin{aligned} & \boldsymbol{Y}_{\mathrm{d}} + \boldsymbol{H} = -\boldsymbol{H}_0 + \boldsymbol{Z}_{\mathrm{old}} \\ \Rightarrow\ & \boldsymbol{Y}_{\mathrm{d}} + \boldsymbol{K}^{\mathrm{T}}\Big[\frac{\partial \hat{\Psi}_{\mathrm{R}}}{\partial \boldsymbol{K}} \circ (\boldsymbol{F}, \boldsymbol{K})\Big] = \boldsymbol{K}^{\mathrm{T}}\Big[\frac{\partial \hat{\mathcal{U}}_{\mathrm{R}}}{\partial \boldsymbol{K}} \circ (\boldsymbol{F}, \boldsymbol{K})\Big] + \boldsymbol{Z}_{\mathrm{old}} \\ \Rightarrow\ & \boldsymbol{Y}_{\mathrm{d}} + \boldsymbol{K}^{\mathrm{T}}\Big[\frac{\partial \hat{\Psi}_{\mathrm{R,eff}}}{\partial \boldsymbol{K}} \circ (\boldsymbol{F}, \boldsymbol{K})\Big] = \boldsymbol{Z}_{\mathrm{old}}, \end{aligned} \tag{48}$$

where we have defined the *effective* Helmholtz free energy density $\hat{\Psi}_{\mathrm{R,eff}} = \hat{\Psi}_{\mathrm{R}} - \hat{\mathcal{U}}_{\mathrm{R}}$ [Grillo et al. 2019a]. Finally, we conclude that, under the hypotheses prescribed above, the activation of an interaction representable by the generalized force $-\boldsymbol{H}_0$ defined in (47) amounts to defining an effective Helmholtz free energy density, which does not alter the medium's Cauchy stress tensor, and renders the dynamic equation for $\boldsymbol{K}$ form-invariant, although not invariant. In other words, the form of the dynamic equation for $\boldsymbol{K}$ remains the same, at the price of redefining the Helmholtz free energy density of the medium [Crevacore et al. 2019; Grillo et al. 2019a]. A direct consequence of this result is that (37) takes on the additional term $-\mathrm{tr}\,\boldsymbol{H}_0$, as in (45).

7. Conclusions

In this work, we have reported on an approach to volumetric growth, which we have termed the "a posteriori approach". While the procedure leading to the initial and boundary value problem in (36a)–(36f) is an elaboration of the theory of [DiCarlo and Quiligotti 2002], our study presents four results that, in our opinion, may contribute to deepen the understanding of some features of the mechanics of growth.

The generalized force $\boldsymbol{Z}$. According to our interpretation of the ideas of [DiCarlo and Quiligotti 2002], in the a posteriori approach depicted in our work, $\boldsymbol{Z}$ plays a very relevant role in the definition of the growth law $R_\gamma \equiv \mathrm{tr}(\boldsymbol{K}^{-1}\dot{\boldsymbol{K}})$. However, we speak of "our interpretation" because, in the work [DiCarlo and Quiligotti 2002], this condition is not addressed explicitly, although the authors mention a condition that rejoins the constitutive character of $\boldsymbol{K}$ (in our notation) with its kinematic one. The importance of $\boldsymbol{Z}$ in biomechanical problems has been emphasized also by DiCarlo [2005], and, on his trail, our study suggests a possible expression for this generalized force that, as shown in Section 4, aims at capturing how the biochemical interactions occurring in a tumor may be turned into a mechanical force, as long as they produce virtual work on $\boldsymbol{K}^{-1}\delta\boldsymbol{K}$ (see [Grillo and Di Stefano 2023b]).

The importance of the Eshelby stress tensor. As reported in Remarks 2 and 3, the Eshelby stress tensor contributes directly and actively to determine the growth law and the sign of R_γ, thereby establishing whether there occurs mass accretion or resorption. Hence, the Eshelby stress tensor plays a crucial role on the growth problem as a whole. This behavior, however, is of purely mechanical origin and, as such, it should be related to the part of the overall variation of the body's mass that is due to the evolution of the *"material inhomogeneities"* of the body itself [Epstein and Maugin 2000]. In other words, this contribution to the variation of mass should be interpreted, for example, as due to mechanisms of mass transfer or transport occurring at a lower scale of the body, rather than as the growth directly related to genetic, epigenetic, or chemo-mechanical factors. Clearly, it is possible to rescale or switch off the term $-\mathrm{tr}[\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K})]$ in (37) by means of an *ad hoc* choice of $\{\hat{\mathfrak{a}}_\nu \circ \omega + 2\,[\hat{\mathfrak{b}}_\nu \circ \omega]\}$. This, however, is a topic addressed in another work [Grillo and Di Stefano 2023a].

The force $\boldsymbol{Z}$ *and the homeostatic stress.* Looking at (35a), or (36d), the role of the Eshelby stress tensor could be reconsidered if $\boldsymbol{Z}$ were redefined as $\boldsymbol{Z}_{\text{new}}$, and expressed by

$$\hat{\boldsymbol{Z}}_{\text{new}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \operatorname{Grad}\omega, \mathcal{X}, \mathcal{T}) := \tfrac{1}{3}[\mathrm{tr}\,\boldsymbol{H}_{\text{target}}]\boldsymbol{I}^{\mathrm{T}} + \hat{\boldsymbol{Z}}_{\text{old}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \operatorname{Grad}\omega), \tag{49}$$

where $\hat{\boldsymbol{Z}}_{\text{old}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega, \operatorname{Grad}\omega)$ is given in (10), $\mathrm{tr}\,\boldsymbol{H}_{\text{target}}$ is a *target* value of stress, and the dependence of $\hat{\boldsymbol{Z}}_{\text{new}}$ on $\mathcal{X}$ and $\mathcal{T}$ is accounted for because $\boldsymbol{H}_{\text{target}}$ may depend explicitly on material points and time. Indeed, we meet similar laws in some studies concerning growth, like, for example, those conducted in [Olsson and Klarbring 2008]. Applying such kind of laws to our context, under the hypothesis of constant generalized viscosities a_ν and b_ν, and in the specific case in which $\omega = \omega_{\text{cr}}$, with ω_{cr} uniform, would lead to $\boldsymbol{Z}_{\text{old}} = \boldsymbol{0}$, and would transform (37) into

$$R_\gamma \equiv \mathrm{tr}(\boldsymbol{K}^{-1}\dot{\boldsymbol{K}}) = \frac{\mathrm{tr}\,\boldsymbol{H}_{\text{target}} - \mathrm{tr}[\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K})]}{J_{\boldsymbol{K}}\{a_\nu + 2b_\nu\}}, \tag{50}$$

where $\mathrm{tr}\,\boldsymbol{H}_{\text{target}}$ acquires the meaning of *"homeostatic stress"* (see [Olsson and Klarbring 2008]), and $\boldsymbol{H}_{\text{target}}$ can be understood, for example, as an *"optimal"* distribution of the Eshelby stress tensor in the medium under study, possibly depending on interactions of biomechanical nature or of other type. This way, the growth law would be driven by the stress unbalance on the right-hand side of (50), and one would have the switching off of the growth law for those values of $\boldsymbol{F}$ and $\boldsymbol{K}$, if they exist, that make the right-hand side of (50) null. This, in general, would lead to nontrivial values of $\boldsymbol{K}$ also for constant, but nonnull, tensors $\boldsymbol{H}_{\text{target}}$. Although an approach of this type is often employed in the context of remodeling, and we do not reject it altogether for growth, we opt for not following it in our work. We make this choice because, unless $\mathrm{tr}\,\boldsymbol{H}_{\text{target}}$ is related to the chemistry of the medium under study in an effective manner, considering $\mathrm{tr}\,\boldsymbol{H}_{\text{target}}$ would lead to an additional contribution to R_γ solely due to mechanical agents, i.e., the difference between $\mathrm{tr}\,\boldsymbol{H}_{\text{target}}$ and $\mathrm{tr}[\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K})]$. In fact, replacing $-\mathrm{tr}[\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K})]$ with $\mathrm{tr}\,\boldsymbol{H}_{\text{target}} - \mathrm{tr}[\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K})]$ is equivalent to redefining the homeostatic stress, i.e., to additively rescale the Eshelby stress tensor, without changing the physical nature of these quantities, which continue to be the generalized forces work-conjugated with the evolution of the *"material inhomogeneities"* [Epstein and Maugin 2000]. For this purpose, we highlight that, independently of $\operatorname{tr} \boldsymbol{H}_{\text{target}}$, the right-hand side of (50) brings about that, for $\omega = \omega_{\text{cr}}$ (which implies $\hat{\boldsymbol{Z}}_{\text{old}} \circ (\boldsymbol{F}, \boldsymbol{K}, \omega_{\text{cr}}, \boldsymbol{0}) = \boldsymbol{0}$), R_γ represents a variation of mass exclusively due to the redistribution of material inhomogeneities within the body. Clearly, in the case of vanishing $\boldsymbol{H}_{\text{target}}$, the value of the homeostatic stress would be that of null Eshelby stress.

It is worth providing a last comment about (50) and its connection with Remark 4. To this end, by setting $\mathcal{H}_{\text{t}} := \frac{1}{3}[\operatorname{tr} \boldsymbol{H}_{\text{target}}]$, and assuming $\boldsymbol{Z}_{\text{old}} = \boldsymbol{0}$ (so that $\boldsymbol{Z}_{\text{new}}$ reduces to $\boldsymbol{Z}_{\text{new}} = \mathcal{H}_{\text{t}} \boldsymbol{I}^{\text{T}}$) and $\mathcal{H}_{\text{t}}$ to be independent of $\boldsymbol{K}$, one can conclude that there exists a potential density function $\mathcal{U}_{\text{Rt}} = \hat{\mathcal{U}}_{\text{Rt}} \circ (\boldsymbol{K}, \mathcal{X}, \mathcal{T}) := \mathcal{H}_{\text{t}} \log(\det \boldsymbol{K})$, such that $\mathcal{H}_{\text{t}} \boldsymbol{I}^{\text{T}} = \boldsymbol{K}^{\text{T}}[\partial_{\boldsymbol{K}} \hat{\mathcal{U}}_{\text{Rt}} \circ (\boldsymbol{K}, \mathcal{X}, \mathcal{T})]$ and (9) becomes

$$\boldsymbol{Y}_{\text{d}} + \boldsymbol{H} = \mathcal{H}_{\text{t}} \boldsymbol{I}^{\text{T}} \;\Rightarrow\; \boldsymbol{Y}_{\text{d}} + \boldsymbol{K}^{\text{T}} \Big[\frac{\partial \hat{\Psi}_{\text{Rt,eff}}}{\partial \boldsymbol{K}} \circ (\boldsymbol{F}, \boldsymbol{K}, \mathcal{X}, \mathcal{T}) \Big] = \boldsymbol{0}, \tag{51a}$$

$$\hat{\Psi}_{\text{Rt,eff}} \circ (\boldsymbol{F}, \boldsymbol{K}, \mathcal{X}, \mathcal{T}) := \hat{\Psi}_{\text{R}} \circ (\boldsymbol{F}, \boldsymbol{K}) - \hat{\mathcal{U}}_{\text{Rt}} \circ (\boldsymbol{K}, \mathcal{X}, \mathcal{T}), \tag{51b}$$

where the composition of $\hat{\mathcal{U}}_{\text{Rt}}$ also with $\mathcal{X}$ and $\mathcal{T}$ accounts for the fact that $\mathcal{H}_{\text{t}}$ depends, in general, on material points and time. By transforming the Helmholtz free energy density as in (41) of Remark 4, (51a) and (51b) transform as

$$\boldsymbol{Y}_{\text{d}} + \boldsymbol{H} + \boldsymbol{H}_0 = \mathcal{H}_{\text{t}} \boldsymbol{I}^{\text{T}} \;\Rightarrow\; \boldsymbol{Y}_{\text{d}} + \boldsymbol{K}^{\text{T}} \Big[\frac{\partial \tilde{\Psi}_{\text{Rt,eff}}}{\partial \boldsymbol{K}} \circ (\boldsymbol{F}, \boldsymbol{K}, \mathcal{X}, \mathcal{T}) \Big] = \boldsymbol{0}, \tag{52a}$$

$$\tilde{\Psi}_{\text{Rt,eff}} \circ (\boldsymbol{F}, \boldsymbol{K}, \mathcal{X}, \mathcal{T}) := \hat{\Psi}_{\text{Rt,eff}} \circ (\boldsymbol{F}, \boldsymbol{K}, \mathcal{X}, \mathcal{T}) + \hat{\Psi}_{\text{R0}} \circ \boldsymbol{K}, \tag{52b}$$

with $\boldsymbol{H}_0 := \boldsymbol{K}^{\text{T}} \partial_{\boldsymbol{K}} [\hat{\Psi}_{\text{R0}} \circ \boldsymbol{K}]$. Therefore, the dynamic equation for $\boldsymbol{K}$ is form-invariant, but not invariant, and R_γ acquires an additional term due to $\frac{1}{3} \operatorname{tr} \boldsymbol{H}_0$:

$$R_\gamma = \frac{\operatorname{tr} \boldsymbol{H}_{\text{target}} - \operatorname{tr}[\hat{\boldsymbol{H}} \circ (\boldsymbol{F}, \boldsymbol{K})] - \operatorname{tr} \boldsymbol{H}_0}{J_{\boldsymbol{K}} \{a_\nu + 2 b_\nu\}}. \tag{53}$$

The nonspherical part of $\boldsymbol{K}$ *and* R_γ. In the mechanics of tumor growth, it is often assumed from the outset that the growth tensor is spherical (see, e.g., [Ambrosi and Preziosi 2009; Mascheroni et al. 2018; Di Stefano et al. 2018; Giverso and Preziosi 2019]). In the present work, however, the growth tensor $\boldsymbol{K}$, computed by means of the initial and boundary value problem (36a)–(36f), *is not* spherical, in general. In fact, this means that, even in the case of an isotropic medium, there exist preferred directions along which the varying mass redistributes itself within the tumor, and the material inhomogeneities evolve. It is the scope of another work [Grillo and Di Stefano 2023a] to show that, in principle, a nonspherical growth tensor, and the preferred directions of growth possibly related to it are ascribable to $\boldsymbol{H}$ and $\boldsymbol{Z}$. To us, this is a potentially major difference between our model of growth and those proposed by other authors, who prescribe the growth tensor to be nonspherical by specifying its properties a priori. In some works, for instance, depending on the problem addressed, the growth tensor is assumed to be transversely isotropic, or orthotropic (see, e.g., [Lubarda and Hoger 2002; Ambrosi et al. 2011; 2019]). In our model, instead, we do not supply any prescription, since we obtain $\boldsymbol{K}$ as an outcome of the IBVP, whose solution is influenced by $\boldsymbol{H}$ and $\boldsymbol{Z}$ [Grillo and Di Stefano 2023b]. Hence, all a priori hypotheses should be associated with the constitutive framework, with the external force $\boldsymbol{Z}$, and with the initial condition on $\boldsymbol{K}$, if required. All this, however, still needs to be tested and compared with the results of others. Here, for the time being, we simply recall that a nonspherical growth tensor $\boldsymbol{K}$ produces a nonspherical rate $\boldsymbol{K}^{-1}\dot{\boldsymbol{K}}$, whose deviatoric part is usually associated with remodeling (see, e.g., [Preziosi et al. 2010]).

Whereas the considerations about the sign of R_γ have been discussed in Remark 3, we emphasize that, within the a posteriori approach presented here, growth is not a direct consequence of the nutrients' availability, although the nutrients play a fundamental role. Hence, the overall framework in which growth is described does not rely on the relation between the "effect" (growth or resorption) and the "cause" (the concentration of nutrients being above or below a critical threshold). Rather, the phenomenon of growth is the kinematics — in a generalized sense — necessary for maintaining the force balance (35a), in which we have the competition or cooperation of purely mechanical contributions (the Eshelby stress tensor) and those that convert chemical interactions into mechanical ones (the generalized force $\boldsymbol{Z}$). Hence, the role of the control parameter associated with the nutrients' mass fraction is made weaker than that played in the approaches based on growth laws supplied phenomenologically a priori.

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