On the Role of Autonomous Control in Organ Development

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Developmental biology (“development” for short) deals with how the mature animal or plant results from a single fertilized cell. This paper is concerned with one aspect of development, morphogenesis—the formation of complex shapes from simpler ones. In particular, this paper focuses on organ development and illustrates the central role that mechanical feedback plays in effecting the final shape of various organs. The first aim of this paper is to illustrate how self-governing autonomous control systems can lead to the development of organs such as the heart. Although feedback plays a key role in these processes, the field is largely unexplored by controls engineers; hence, the second aim of this paper is to introduce mechanical feedback during development to controls engineers and suggest avenues for future research. [DOI: 10.1115/1.4024996]

1 Introduction

The role of feedback in the mature human body is well-studied and well-appreciated. For a good overview of the topic, please see Chapter 1 of the classic text Vander’s Human Physiology [1]. A classic example is body temperature control where an internal temperature set point of 37 °C is maintained irrespective of environmental factors. We refer to 37 °C as a relatively stable set point because minor fluctuations are permitted, and certain conditions such as a fever, when the body is fighting off infection, require a higher set point.

This paper considers set point regulation during biomechanical feedback, i.e., stress and strain information are fed back to effect some necessary mechanical action. A classic example—and one that illustrates the importance of positive feedback in the human body—is uterine contractions during parturition (childbirth). The stretching of the cervix (the opening of the uterus) induces uterine contractions, which stretch the cervix even more leading to stronger contractions. This positive biomechanical feedback, along with other hormonal positive feedback mechanisms, is vital for proper conclusion of labor and childbirth [1–3].

While biomechanical feedback in mature animals and humans has been studied extensively, relatively little is known about its effects during embryonic development. During development, many of the familiar organs change shape dramatically. This process is known as morphogenesis (from Greek *morphe*, shape, and *genesis*, creation, literally creation of shape). The heart, for instance, starts out as a straight tube before bending and twisting in a complex process called “looping” until the familiar four-chambered pump is realized [4].

Developmental processes can be divided into sequential morphogenetic (i.e., shape change) events. Each of these morphogenetic events has a distinct initial shape and a distinct final shape. For instance, in early cardiac looping, the initial shape is a straight cylindrical tube while the final shape is a curved tube. This process is called “c-looping” because the final shape resembles the letter “c.” There are a variety of mechanical processes that can

transform a straight tube into a c-shaped tube; but the interesting point is that the final shape is distinct. Once the “c”-shaped tube is obtained, bending stops (Fig. 1). Like the temperature control example, the embryo somehow has a sense for the correct final shape (which can be thought of as a set point). This paper will explore some control strategies that the embryo can employ to sense the correct final shape. It was previously thought that genes micromanage the whole process; but, recent evidence indicates that genes play a more supervisory role while a variety of morphogenetic mechanisms are self-regulatory [5–7].

Using early heart development as an example, this paper will demonstrate the role of feedback control in morphogenesis. First, we will introduce the biological basics of this remarkable shape change (Sec. 3.1). Then, we will explain how simple stress feedback can lead to that shape change (Sec. 3.2) and discuss how concepts in control theory can be used to better understand this process (Sec. 4). To present an overview of the mathematics involved, we also provide a simple example where feedback and stability analysis can be considered analytically without resorting to numerical simulations (Sec. 5). In the remainder of this paper, the term “development” denotes formation of an organ from its embryonic precursor and the term “morphogenesis” denotes shape change during development.

2 Methods

All experimental data presented in this paper are from the author’s laboratory. The chicken embryo, whose heart development is similar to that in humans, is used as the experimental model. The details of the incubation procedure and other experimental details are found in Ref. [8], and this paper will focus only on those results that are of interest to the controls community.

Finite element (FE) modeling is widely used to study morphogenesis. All models used in this paper were done in ABAQUS. This paper concentrates on the control theory aspects of morphogenesis and FE details such as element selection, material characterization, and convergence can be found in Ref. [9]. For the constrained column example shown in Sec. 5, state propagation of the nonlinear differential equation was done in SIMULINK.

3 Results

3.1 Morphogenesis During Early Heart Development. The heart is the first functioning organ in the developing embryo, and blood flow becomes increasingly important as development

Fig. 1 Cardiac c-looping in the chick embryo with hearts shown enclosed in the dotted rectangle. At 36 h of incubation (a), the chick heart is simply a straight tube flanked by the primitive atria. At 48 h of incubation (b), the straight tube is transformed into a c-shaped tube. Note the dramatic increase in curvature of the heart tube (indicated by arrows), which results in the first major break of left-right symmetry in the developing embryo. C = conotruncus (outflow tube), V = primitive ventricle, A = primitive atrium. Scale bar = 300 μ m.

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proceeds. A thorough overview of heart formation is found in Ref. [4], and the biophysical mechanisms discovered to date are summarized in Ref. [10]. Here, we will focus on the possible role of biomechanical feedback in effecting shape change during c-looping.

The primitive heart is little more than a simple straight tube (Fig. 1(a)). After 12 h of development, this tube is bent into a c-shaped tube (Fig. 1(b)). It is important to note that the curved shape in Fig. 1(b) acts as a set point, i.e., although curvature is dramatically increased (indicated by arrows in Figs. 1(a) and 1(b)), this is a stable system with no overshoot. In other words, bending does not continue indefinitely; once the curvature in Fig. 1(b) is reached, bending ceases and the next phase of heart development is initiated.

3.2 Biomechanical Feedback During Heart Development.

How does the embryonic heart know that the correct shape has been reached and that bending must cease? Since tissues can sense stress [11–13], one possibility is that genes specify a target stress field, $\sigma^*(\mathbf{x})$, which corresponds to the bent shape in Fig. 1(b). The stress error, i.e., the difference between the actual stress, σ , and the target stress, σ^* , drives morphogenesis [9]. This idea is captured in Fig. 2.

The scheme is captured mathematically using a simple differential equation [9]:

$$\dot{\lambda}_g(t)/\lambda_g(t) = a(\sigma(t) - \sigma^*) \quad (1)$$

where $\sigma(t)$ and σ^* are the values of the current and target stress, respectively, and λ_g is the growth stretch ratio. A λ_g value of 1.2 instructs the cell-level processes to expand the local tissue by 20% and a value of 0.8 results in a 20% contraction. According to Eq. (1), when $\sigma(t) = \sigma^*$, $\dot{\lambda}_g = 0$, and the current shape is maintained. Note that all quantities are field variables, and their evolution is distinct at each material point. We consider the simple case where the target stress field, $\sigma^*(\mathbf{x})$, is fixed in time. Once a certain morphogenetic phase is completed, the next phase can be initiated by changing $\sigma^*(\mathbf{x})$, possibly by gene action.

We illustrate the above morphogenetic law by modeling embryonic heart bending as bending in a simple cantilever beam. FE analysis is used to obtain the results. A target stress of 1 unit is specified in the bottom half of the beam while the top half of the beam has no target stress specified (i.e., a is zero here, there is no feedback, and loop in Fig. 2 is open). The results are shown in Fig. 3.

According to Eq. (1), with all initial conditions set to zero and the target stress distribution as specified in Fig. 3(a), the bottom half of the beam wants to contract, while the top half is simply passive and does not want to change shape. This arrangement is geometrically incompatible and energetically unfavorable; therefore, the beam will bend. The remarkable result is that autoregulation is built into this simple set up and the beam bends until the desired stress distribution is reached (Figs. 3(a) and 3(b)). Once the target stress is reached in the bottom of the beam, $\sigma(t) = \sigma^*$ here (Fig. 3(c)), and according to Eq. (1), $\dot{\lambda}_g(t) = 0$, and there is no further stimulant for bending. A plot of stress distribution across the beam section shows that the stresses in the passive portion (top of the beam) self-equilibrate in order to satisfy the constant stress requirement in the bottom of the beam (Fig. 3(d)).

Even though not the sort covered in standard textbooks on feedback control, the above system demonstrates how simple proportional feedback (of stress) can be used to achieve a set point (i.e., desired shape). Similar to a traditional control system, the system can be rendered unstable or marginally stable by introducing an appropriate delay in the feedback path (results not shown).

To illustrate the basic concepts, we have applied the morphogenetic law (Eq. (1)) to a cantilever beam. When the same law is

Fig. 2 Morphogenesis effected using stress feedback. Morphogenesis (shape change) continues till the shape corresponding to the target stress field is attained. The “stress error,” i.e., the difference between the actual stress (σ) and the target stress (σ^*) drives morphogenesis via various cell-level processes such as growth, cytoskeletal contraction, cell shape changes, etc. σ , σ^* , and a , the proportional gain are field variables whose values change with position. Once a certain shape is reached, genes can then modify σ^* to initiate the next phase of morphogenesis. Please note that a pure proportional control topology is used. The system reacts to the instantaneous error and there is no integral or derivative action. Please see text for a mathematical description. Please also see Appendix for details on how biological processes such as growth and cytoskeletal contraction are modeled mathematically. (Modified from Ref. [9]; used with kind permission from Springer.)

applied to a FE model of a straight embryonic heart tube, the model-predicted final curved shape, and sequence of shapes closely match those in experiment. Two points are noteworthy here: (1) embryonic heart bending is robust. Similar to a good control system, secondary mechanisms kick in when the primary actuators are disrupted [14,15]. (2) It is not just final shape that matters; correct realization of all the intermediate shapes is just as important for the health of the embryo. Hence, the desired “signal” from a control standpoint should be thought of as a continuum of shapes.

4 Discussion

The formation of a fully functional organism from a single fertilized egg is one of the more complicated problems to analyze. The laws of physics are usually applied to cases where the number of variables is small, e.g., the laws of classical thermodynamics, electromagnetics, etc. [5,6]. Long years of evolution, however, have ensured that literally thousands of variables are involved in the development of an organism. Nonetheless, by restricting our attention to a specific section of development, i.e., shape changes in tubular structures during organ development, as was done in this paper, we can formulate mathematical laws that explain morphogenesis.

4.1 Role of Control Theory. The controls community currently has no involvement in formulating morphogenetic feedback laws. Because of this, some important concepts get overlooked:

- (1) All feedback is assumed to be purely proportional. As seen in Eq. (1), integral and derivative controls are completely ignored even in these simple topologies. In particular, integral control seems to be implicated since the “steady-state error” in normal morphogenesis is nearly always zero, even in the presence of perturbations. An intriguing example is found in Ref. [14]. Here, the mechanisms that normally control cardiac c-looping (Sec. 3) were disrupted. Even though normal looping did not occur for the first 6 h, the correct shape was attained at the end of 12 h, suggesting a role for control action activated by error accumulation, i.e., integral control.
- (2) All feedback is assumed to be instantaneous, and the effect of any transport delay is ignored. Delay is a key player in biology with causes and effects often separated by time. The controls community has considerable expertise in dealing with delay (including time-varying delay, which is important in development) in complex systems [16]. This

¹In the next phase, the primitive atrium (part marked “A” in Fig. 1) moves to its definitive position above the primitive ventricle (part marked “V” in Fig. 1). This phase is called “s-looping.” Please see Ref. [4] for details.

Fig. 3 Morphogenetic regulation in a cantilever beam. A target stress ($\sigma^* = 1.0$) is specified in the bottom half of the beam while the top half remains passive. This arrangement leads to a curved beam (a). What is remarkable is that the beam curvature (κ) increases only until a specific shape is reached (b). At this point, the target stress distribution specified in (a) is reached and the beam ceases to bend. A plot of stress in a representative element at the bottom (indicated by the solid square in (a)) also shows a steady rise until steady-state reached (c). Stress across the beam section (indicated by the solid line in (a), going from bottom to top) shows that the stress in the passive portion (top of the beam) self-equilibrates in order to satisfy the constant stress requirement in the bottom of the beam (d). (Modified from Ref. [9]; used with kind permission from Springer.)

expertise will be useful when studying feedback in the embryo.

- (3) Stability is not analyzed thoroughly and formally. As is typical for nonlinear systems, initial conditions and boundary conditions play a major role in stability [17,18]. Formal analysis of stability is needed to better characterize the proposed feedback systems.
- (4) The forms of the morphogenetic laws considered are rather simplistic. As more experimental data become available, there is a strong need for better mathematical formulations. In the heart looping example that we considered, the target stress distribution was directly specified, presumably by genetic processes. Recently, researchers have suggested a further decoupling from genetic control [19,20], but the morphogenetic laws are again simplistic involving just proportional control.

To illustrate the new insights that can be obtained by applying the tools of control theory, consider the phase portraits shown in Fig. 4. Phase portraits are shown for the simple stress feedback case discussed in Sec. 3.2, where a constant target stress ($\sigma^* = 1.0$) was specified in the bottom half of a cantilever beam, and it was found that the beam bent till the target stress was realized (Fig. 3). The phase plane plots show results of the same simulation run with different initial conditions. It is seen that irrespective of the initial conditions, the system converges to a stable node (marked by the point labeled “SN” in the Fig. 4, $\sigma = \sigma^* = 1.0$, $\lambda_g = 0.81$) where the actual stress and target stress are equal. Indeed, we see an entire region of convergence in the phase plane (indicated by the dotted box in Fig. 4) where the responses are indistinguishable. This kind of convergent behavior is actually seen in heart development. While young hearts have considerable variability in shape and size, the amount of variability in older hearts is smaller. This insight is missed if phase plane analysis is not done.

Phase portraits also help illustrate a crucial concept in development, *emergence* [6]. This is the arising of complex behaviors from simple operations. The morphogenetic law used in Sec. 3.2, Eq. (1), is quite simple. Yet, it leads to an autonomous response in embryonic heart morphogenesis. Furthermore, the law predicts the presence of a convergent region (Fig. 4).

Traditional control theory concepts have been developed with machines and industrial applications in mind, and the application of control theory to problems in biology (where natural biological variation is a key issue) is relatively new. It is hoped that this paper will stimulate interest in this field among controls engineers and tools such as Lyapunov’s direct method and phase plane analysis are employed to develop the existing morphomechanical laws and propose new ones.

Fig. 4 Phase plane portrait for the morphogenetic feedback mechanism discussed in this paper. A cantilever beam is used in all simulations (Sec. 3.2). Note that the system converges to a stable node (marked “SN”) irrespective of initial conditions. Actually, there is an entire region of convergence in the phase plane (indicated by the dotted box) where the responses are indistinguishable. This sort of convergent response is often found during development (please see text for details).

For the benefit of interested controls engineers, we present, in Sec. 5, a simple example for which the analytical solution is known. We use the same morphogenetic law as in Eq. (1) and consider a case where the stress equation is easily derived. We then close the loop and analyze stability.

4.2 Role of Genes. It is helpful to think about a simple analogy when considering the role of genes in embryo development. Consider a group of people who want to build a house. These owners of the future house then hire various contractors to do the actual building. Now, it is certainly true that the owners are the prime movers behind the construction of this house, i.e., if the owners were somehow incapacitated, then the house will not be built. The owners, however, usually do not know much about actual house building and rely on the contractors to do the job for them.

Now, if one is studying house building, statements such as “the owners determine many of the features of the house” and “the owners are directly responsible for getting the house built” are certainly true. Yet, from a scientific stand point, these statements, although true, are grossly incomplete, and come nowhere close to answering the question “how does the house get built?”

Similarly, genes certainly exercise supervisory control over many morphogenetic processes and knocking out certain genes will halt several morphogenetic processes. However, morphogenesis is a complex four-dimensional (three spatial + time) process and the mechanism of gene action needs to be known in order for our understanding to be complete. This idea is covered in more detail in Refs. [5] and [6]. For a more philosophical treatment, please see Ref. [7].

Hence, there is a need for engineering principles to be applied to morphogenesis and to figure out exactly how the plan laid out by the genes is translated to actual shapes in the embryo. Several researchers in genetics indeed support this argument. In the words of biologist Jamie Davies [6]:

“They [knowledge of molecular and genetic pathways] provide a useful summary of key processes, but they have almost no predictive power except in the crude sense of predicting what knockouts would cause morphogenesis to fail... Quantitative modeling, which nowadays means computer modeling of the morphogenetic process in real embryos, promises to be one of most powerful means of understanding morphogenesis we will have in the near future”

This paper proposes *biomechanical stress feedback* as a possible mechanism to translate genetic instructions into specific embryonic shapes. One must, however, be careful when applying computer modeling to study problems in morphogenesis. Similar to the examples considered in this paper, the morphogenetic feedback laws should be (1) suggested by experimental data and (2) verifiable by experiments.

4.3 Role of Experiments. The following is a quote attributed to John von Neumann [6]:

“Give me four parameters, and I can fit an elephant. Give me five, and I can wiggle its trunk”

When a computer model has several parameters, it is not difficult to adjust these parameters to get a shape that matches the final shape observed in experiment. Furthermore, the set of parameters chosen will not be unique in that more than one permutation will generate the experimental shape. To avoid these pitfalls, two courses of action are recommended:

- (1) Compare model-predicted *local* data with that of experiments. Local data can include stress and strain fields, and for those models that include them, various chemical gradients. While several permutations of the same parameters can lead to the same *global* shape, it is unlikely that all will lead to the same *local* fields.
- (2) When feedback control is involved, it is important to consider the *time history* of the local field quantities. For example, biomechanical feedback considered in Sec. 3.2 predicts

an exponential rise in the beam curvature that quickly converges to the correct value (Fig. 3(b)). The corresponding longitudinal strain would also be expected to follow this pattern and indeed it does [21].

5 Growth in a Constrained Column

To explain the basic concepts involved in growth and morphogenesis, we present a simple example. We consider stress feedback in a column (Fig. 5) that is fixed at both ends. This situation sometimes arises in development [19]. As in the heart development example, we specify an axial target stress (σ_x^*) and the column grows until this stress is attained. Please note that “growth” here may also include a decrease in length, i.e., atrophy or contraction. The governing equations for this system are given by

$$\frac{\dot{\lambda}_{gx}}{\lambda_{gx}} = a(\sigma_x - \sigma_x^*) \quad (2)$$

$$\sigma_x = 2C \left(\frac{1}{\lambda_{gx}^2} - \lambda_{gx} \right) \quad (3)$$

where Eq. (2) is simply the previously considered feedback law, Eq. (1), with growth specified in the x -direction and Eq. (3) is the axial stress when the column grows by λ_{gx} . $a > 0$ is a constant in the feedback law and C is a material parameter equivalent to the modulus. Please see Appendix for the derivation of Eq. (3).

Substituting the equation for stress, Eq. (3), into the morphogenetic law, Eq. (2) yields the following first order nonlinear differential equation:

$$\dot{\lambda}_{gx} = -2aC\lambda_{gx}^2 - a\lambda_{gx}\sigma_x^* + \frac{2aC}{\lambda_{gx}} \quad (4)$$

We can now show that this equation has a single, stable equilibrium point, which occurs when $\sigma_x = \sigma_x^*$, i.e., $\dot{\lambda}_{gx} = 0$ per Eq. (2). Setting Eq. (4) to zero yields

$$\lambda_{gx}^3 + \frac{\lambda_{gx}^2\sigma_x^*}{2C} - 1 = 0 \quad (5)$$

Define the residual function and its derivative

$$f(\lambda_{gx}) = \lambda_{gx}^3 + \frac{\lambda_{gx}^2\sigma_x^*}{2C} - 1 \quad (6)$$

$$\frac{df}{d\lambda_{gx}} = 3\lambda_{gx}^2 + \frac{\lambda_{gx}\sigma_x^*}{C} \quad (7)$$

and note the following: (1) $C \geq 0$ because it is a material property equivalent to the modulus; (2) λ_{gx} is a ratio of lengths and is also always positive; and (3) since we are considering a positive target stress, σ_x^* is also always positive. With these facts, we observe the following:

$$f(0) = -1 \quad (8)$$

$$\frac{df}{d\lambda_{gx}} > 0 \quad (9)$$

$$\lim_{\lambda_{gx} \rightarrow \infty} f(\lambda_{gx}) = \infty \quad (10)$$

Hence, when f is plotted as a function of λ_{gx} (with λ_{gx} ranging from zero² to ∞ , i.e., all the values that λ_{gx} can possibly take), it starts below zero for small λ_{gx} (Eq. (8)) and ends up above zero

²Since λ_{gx} is the ratio of new length to the old length, it can never actually be zero. It can, however, get arbitrarily close to zero when the new length is a small fraction of the old one.

Fig. 5 Growth in a constrained column. The cartoon on top illustrates the process. Growth here can be thought of as a two-step process. In the first step, the boundary conditions are released and the column of original length L_0 is allowed to grow freely. This stress-free process produces a column of greater length, L . In the next step, compressive forces due to the boundary conditions are imposed to bring the length back to L_0 . The growth stretch ratio is defined as $\lambda_{gx} = L/L_0$. Please note that for negative growth (atrophy), $L < L_0$ and hence $\lambda_{gx} < 1$. In this case, the column shrinks first and then is expanded by the end forces due to the boundary condition. Buckling is ignored and boundary constraints apply only in the x -direction; the beam is free to move in the y - and z -directions (z -direction is out of the page). Graph (a) shows a plot of $\dot{\lambda}_{gx}$ versus λ_{gx} (Eq. (4)) with $C = a = 1.0$ and $\sigma_x^* = 2.0$. Graph (b) shows the time trace of λ_{gx} according to Eq. (4) for various initial conditions. The system converges to a stable equilibrium point, $\lambda_{gx}^E \approx 0.8$.

for large λ_{gx} (Eq. (10)). Since the slope of this curve is always positive (Eq. (9)), there is exactly one and only one zero crossing. Hence, the equilibrium point corresponding to $\sigma_x = \sigma_x^*$ in Eq. (2) is unique. Let $\lambda_{gx} = \lambda_{gx}^E$ at the equilibrium point.

We can show that the equilibrium point is stable by differentiating Eq. (4) with respect to λ_{gx} to get

$$\frac{d\dot{\lambda}_{gx}}{d\lambda_{gx}} = -4aC\lambda_{gx} - a\sigma_x^* - \frac{2aC}{\lambda_{gx}^2} \quad (11)$$

All three terms in the right-hand side are negative, and hence $\dot{\lambda}_{gx}/\lambda_{gx}$ is always negative, including at the equilibrium point. When $\dot{\lambda}_{gx}$ is plotted against λ_{gx} (Fig. 5(a), $a = C = 1.0$ and $\sigma_x^* = 2.0$), we see that $\dot{\lambda}_{gx} > 0$ for $\lambda_{gx} < \lambda_{gx}^E$ and $\dot{\lambda}_{gx} < 0$ for $\lambda_{gx} > \lambda_{gx}^E$. This shows that the equilibrium point is attractive and hence stable. Representative time traces of λ_{gx} (Fig. 5(b)) show that the trajectory converges the stable equilibrium point ($\dot{\lambda}_{gx} = 0$, $\lambda_{gx}^E \approx 0.8$) irrespective of initial conditions.

6 Concluding Remarks

Control theory deals with manipulating an actual signal to match a desired signal. Usually, this is done using a control algorithm. In the problems considered here, the desired signal is a sequence of shapes that the embryonic organs must transition through. The sheer complexity of the shape changes and the robustness through which they are accomplished eliminate open loop systems and argue strongly in favor of feedback control.

Three areas of expertise are needed to properly analyze the control systems involved in development: (1) mechanics, (2) developmental biology, and (3) control theory. While professionals in the first two are actively involved in the development of morphogenetic laws, the field is largely opaque to control theory professionals. Yet, this expertise is crucial in light of the complexities involved in morphogenetic feedback.

Although we have focused on heart development, several other organs also undergo complex shape changes during development [22]. Abnormal organ development leads to birth defects and

other congenital anomalies. Proper understanding of the developmental processes will help in the treatment of these diseases.

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Appendix: Derivation of Stress Equation

We provide a brief overview of the mathematics contained in the box labeled “Growth, Cytoskeletal Contraction, Active Cell Shape Changes” in Fig. 2. The approach presented here is based on a multiplicative decomposition of the deformation gradient tensor [23]:

$$\mathbf{F} = \mathbf{F}_e \mathbf{F}_g \quad (A1)$$

where $\mathbf{F}$ is the total deformation gradient tensor and $\mathbf{F}_g$ is the growth tensor. The key point here is that unrestrained homogeneous growth does not lead to stress and hence only the elastic portion of the deformation gradient ($\mathbf{F}_e = \mathbf{F} \mathbf{F}_g^{-1}$) is used in stress calculations. For the 1D constrained column considered here with growth specified only in the x -direction, the tensor equation can be reduced to a scalar equation:

$$\lambda_{xe} = \frac{\lambda_x}{\lambda_{gx}} \quad (A2)$$

where λ_{gx} , the stretch ratio due to growth, is excluded from the overall stretch ratio, λ_x . The result is the elastic stretch ratio, λ_{xe} , which will be used in stress calculations. In the constrained column (Sec. 5, Fig. 5), there is no growth in the y - and z -directions:

$$\lambda_{gy} = \lambda_{gz} = 1.0 \quad (A3)$$

where λ_{gy} and λ_{gz} are the growth stretch ratios in the y- and z-directions, respectively. Using Eq. (A2) with the subscripts y and z leads to

$$\begin{aligned} \lambda_{ye} &= \lambda_y \\ \lambda_{ze} &= \lambda_z \end{aligned} \quad (A4)$$

where λ_{ye} is the elastic part of the stretch and λ_y is the total stretch in the y-direction. Similar remarks apply to the z-direction. The column is constrained only in the x-direction and free to expand in y and z (Fig. 5) directions. Since the material is homogenous and isotropic, symmetry leads to

$$\begin{aligned} \lambda_{ye} &= \lambda_{ze} \\ \lambda_y &= \lambda_z \end{aligned} \quad (A5)$$

Growth obviously involves a change in volume; but many biological materials are incompressible when external loads are applied, i.e., $\lambda_{xe}\lambda_{ye}\lambda_{ze} = 1$. Using this and Eq. (A5) gives

$$\lambda_{ye}^2 = \lambda_{ze}^2 = \frac{1}{\lambda_{xe}} \quad (A6)$$

We assume that the column is made out neo-Hookean material whose strain energy density function is given by $W = C(I_1 - 3)$. Where C is a material constant that is equivalent to the Young's modulus in linear materials. $I_1 = \lambda_{xe}^2 + \lambda_{ye}^2 + \lambda_{ze}^2$ is the first strain invariant. The following are the stress equations [24]:

$$\sigma_x = \lambda_{xe} \frac{\partial W}{\partial \lambda_{xe}} - p = 2C\lambda_{xe}^2 - p \quad (A7)$$

$$\sigma_y = \lambda_{ye} \frac{\partial W}{\partial \lambda_{ye}} - p = 2C\lambda_{ye}^2 - p \quad (A8)$$

$$\sigma_z = \lambda_{ze} \frac{\partial W}{\partial \lambda_{ze}} - p = 2C\lambda_{ze}^2 - p \quad (A9)$$

where p is the incompressibility factor and the simplified expressions are obtained by substituting for W and differentiating. Since the column is not constrained in the y and z directions, $\sigma_y = \sigma_z = 0$. Using Eq. (A8) (we could also use Eq. (A9)), we get $p = 2C\lambda_{ye}^2$. Using this in Eq. (A7) gives

$$\sigma_x = 2C(\lambda_{xe}^2 - \lambda_{ye}^2) \quad (A10)$$

and using Eq. (A6) in (A10) gives

$$\sigma_x = 2C\left(\lambda_{xe}^2 - \frac{1}{\lambda_{xe}}\right) \quad (A11)$$

Since the column is constrained there can be no net stretch in the x-direction, i.e., $\lambda_x = 1$. Using this in Eq. (A2), we get $\lambda_{xe} = 1/\lambda_{gx}$. Using this last in Eq. (A11) yields

$$\sigma_x = 2C\left(\frac{1}{\lambda_{gx}^2} - \lambda_{gx}\right) \quad (A12)$$

Please note: In this example, we have considered growth in the x-direction only (i.e., $\lambda_{gy} = \lambda_{gz} = 1$ and λ_{gx} is specified by the feedback law, Eq. (1)). In the most general case, growth can be independently specified in all three directions. Active cell shape changes are modeled as volume-preserving growth, i.e., $\lambda_{gx}\lambda_{gy}\lambda_{gz} = 1$. While contraction is modeled using volume-preserving growth along with an increase in tissue modulus (the parameter C). Please see Ref. [25] for details on modeling these and other morphogenetic processes.

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