Integral Control of Plant Gravitropism through the Interplay of Hormone Signaling and Gene Regulation

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ABSTRACT The interplay between hormone signaling and gene regulatory networks is instrumental in promoting the development of living organisms. In particular, plants have evolved mechanisms to sense gravity and orient themselves accordingly. Here, we present a mathematical model that reproduces plant gravitropic responses based on known molecular genetic interactions for auxin signaling coupled with a physical description of plant reorientation. The model allows one to analyze the spatiotemporal dynamics of the system, triggered by an auxin gradient that induces differential growth of the plant with respect to the gravity vector. Our model predicts two important features with strong biological implications: 1), robustness of the regulatory circuit as a consequence of integral control; and 2), a higher degree of plasticity generated by the molecular interplay between two classes of hormones. Our model also predicts the ability of gibberellins to modulate the tropic response and supports the integration of the hormonal role at the level of gene regulation.

INTRODUCTION

Living organisms have the ability to sense and process many environmental signals and act accordingly. For this purpose, organisms have developed a potent sensory machinery that, coupled with the appropriate signaling circuits, can trigger specific cellular responses. Therefore, the capacity of an organism to adapt to varying environmental conditions depends on several intrinsic properties established by the topology of the circuits involved in this response. Plants display a particularly good adaptive ability, and it has been proposed that this advantage may rely on the architecture of their signaling networks (1). Among all external stimuli, gravity is invariant, and plants use it as a reference for orientation of the growth of their organs. For instance, plants placed in a horizontal position reorient growth of the aerial part in the direction opposite to the gravity vector. According to the early Cholodny-Went theory (2), the perception of a change of position with respect to the gravity vector triggers the formation of a gradient that determines differential growth rates on either side of the organ, thus causing the formation of a curvature and the reorientation of the whole organ. More recent work has established that this gradient is formed by differential distribution of the phytohormone auxin (3,4). In aerial tissues, auxin accumulation triggers a cascade of molecular events (5–7) that ultimately promote the expression of growth-related genes in one side of the organ subject to the gravitropic stimulus.

Whereas the auxin gradient is instrumental in the differential promotion of growth, the phytohormone gibberellins were recently shown to be involved in regulating the response to gravity (8,9). Gibberellins are well-known growth-promoting hormones (10,11) that sometimes act as a subsidiary signal for auxin (12). However, in the case of the gravitropic response, they display a counterintuitive effect because they delay reorientation, and they do so by attenuating auxin signaling through the transcriptional regulation of an auxin-signaling element (9). On the basis of these findings, we sought to construct a mathematical model to study the combined effect of the two hormones on plant gravitropism and make predictions regarding the expected behavior under different conditions.

Given the complex interactions that modulate the gravitropic response, we attempted to elucidate the quantitative and dynamical properties of the signaling circuit by modeling the molecular interactions that subtend this response. We paid particular attention to the type of control mechanism in the circuit, and the capacity of the circuit to generate noise in gene expression. We also sought to address the intriguing questions of how cell fate is switched by environmental stimuli, and how precise molecular interactions can control the physical behavior of a plant. Here we present a stochastic dynamical model to dissect the particular hormonal interplay between auxins and gibberellins, which is key for plant behavior under gravitropic stimuli. The whole model consists of a molecular description of gene interactions, assumed to be in quasi-steady state, and a physical model that accounts for the reorientation of the plant. We analytically developed the model to illustrate an integral control mechanism and to obtain a theoretical prediction of noise in gene expression.

MODEL AND RESULTS

Molecular level

Although gravitropic reorientation affects a whole organ, including multiple cell types, experimental observations

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led to the assumption that gravity is perceived in the endodermis (9,13), and that the molecular interactions that initially regulate the gravitropic response occur in these cells (Fig. 1 a). Cell expansion is accomplished by expressing growth-related genes (e.g., expansins) that drive the elongation of the plant. These genes are activated by auxin-response transcription factors (ARFs) (14,15), a pivotal family of transcriptional regulators in plants, and repressed by the action of DELLA proteins (9), a family of putative regulators that inhibit cell proliferation and expansion. ARFs also activate transcription of auxin/indole-3-acetic acid-induced (Aux/IAA) proteins (14,15), which implement a posttranslational negative feedback loop that provides robustness to the system (16,17). Although in some cases hormone signals may slightly influence the expression of ARFs (18,19), here we assume that the total amount of ARFs is constant and does not depend on auxins or gibberellins (15). In addition, ARFs and Aux/IAA proteins form homo- and heterodimers, with much faster kinetics for heterodimerization (20). This regulatory loop is closed by the action of auxins, which trigger the degradation of Aux/IAA proteins by the proteasome through the formation of a complex between the hormone, the auxin receptor, and the target Aux/IAA protein (5,21). Hormonal cross talk between gibberellins and auxins emerges because gibberellins repress the synthesis of DELLA proteins, and, as recent investigations have shown, DELLA proteins downregulate Aux/IAA proteins and moderate the response to the auxin gradient induced by gravity (9).

On the basis of these interactions, we constructed a reduced molecular model (Fig. 1 b) defined by differential equations involving the concentration of auxins (x, dimensionless variable), ARFs (u, total amount), Aux/IAA proteins (y), and the generic gene (referred to as expansins in the following) activity executing cell expansion (z). In the model, auxins just promote the degradation of Aux/IAA proteins, and the effect of gibberellins by means of DELLA proteins is reduced to coefficients that modulate the protein synthesis rate. The deterministic dynamics are governed by

\[
\frac{dy}{dt} = \alpha \Gamma y f_1(y) - xy - y, \\
\frac{dz}{dt} = \alpha \Gamma f_m(y) - \frac{1}{\tau} z,
\]

where \(\alpha\) is the maximal synthesis rate; \(\Gamma\) and \(\Gamma_z\) are the repression coefficients of DELLA over Aux/IAA proteins and expansions, respectively; and \(f_1(y)\) and \(f_m(y)\) are the regulatory functions of ARFs. Notice that these functions also depend on \(u_{tot}\). We set variations in the levels of gibberellins by changing the values of \(\Gamma_y\) and \(\Gamma_z\). For normal levels of gibberellins, we set \(\Gamma_y = \Gamma_z = 1\), whereas for low levels of this hormone, DELLA proteins are upregulated and can exert repression, resulting in \(\Gamma_y \leq \Gamma_z < 1\) (we also assume that the repression over Aux/IAA proteins is stronger than that over expansins). Time is conveniently rescaled by the degradation coefficient of Aux/IAA proteins, whereas \(\tau\) accounts for the higher stability of expansins. We assume that auxins do not saturate the proteolytic degradation of Aux/IAA proteins, and that the kinetics of this process is equivalent to that of thermodynamic degradation (21). The values of the model parameters are shown in Table 1.

By exploiting the different timescales (binding reactions are much faster than protein synthesis) and assuming much faster kinetics for heterodimerization \((\mu > \rho)\), we obtain the following expression for the free amount of ARFs:

\[
u(y) = \frac{1}{4\rho} \left( \sqrt{1 + 8\rho(u_{tot} - y)} - 1 \right), \tag{2}
\]

for \(y < u_{tot}\), and \(u = 0\) elsewhere (see Supporting Material). In addition, the transcriptional activation function of ARFs (assumed of Hill-type) reads as

\[
f_1(y) = \frac{u(y)^n}{(hK)^n + u(y)^n}, \tag{3}
\]

where \(n\) is the Hill coefficient, \(K\) is the protein-DNA binding coefficient, and the activation threshold of transcription can be modulated by using different values of \(h\). Herein, we consider \(h = 1\) for Aux/IAA activation, whereas \(h = m\) for expansin activation.

We simulate the model to study the sensitivity of the kinetic parameters in the stationary regime (Fig. 2). The stationary solution is given by \(y_0(1 + 1) = \alpha \Gamma y f_1(y_0)\) and \(z_0 = \tau \alpha \Gamma f_m(y_0)\), where \(y_0\) and \(z_0\) denote the steady-state

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**FIGURE 1** (a) Schematic representation of the genetic network that controls gravitropism in plants. Dotted lines denote transcription regulations. The network involves two central hormones in plant signaling (auxins (AUX) and gibberellins (GAs)), auxin/IAA proteins (Aux/IAA, labeled as IAA), ARFs, DELLA proteins, and cell expansion proteins (EXP). AUX promote the degradation of IAA proteins, and GAs negatively control the synthesis of DELLA proteins. Letters denote the kinetic parameters of the model. (b) Simplified regulatory network involving two genes \(y\) and \(z\) and one hormone \(x\). See the text for a complete explanation. (c) Planar representation of the plant organ. The gravity vector leads to a differential accumulation of auxins, represented by small circles.
values. The level of Aux/IAA proteins is fundamental to determine the functioning point, and this is controlled by three elements in the circuit: auxins, gibberellins (via DELLA proteins), and ARFs. The accumulation of auxins decreases the abundance of Aux/IAA proteins, whereas higher levels of DELLA proteins (modeled by \( \Gamma_y \leq \Gamma_z < 1 \)) boost the expression of expansins and their differential expression (\( V_z \)) computed between the two sides of the elongating plant organ. In fact, the differential growth reaches a maximum at a certain level of DELLA proteins, higher than in the wild-type case. Although DELLA proteins directly repress the expansion genes, their action over the self-repressed Aux/IAA proteins counteracts that effect. Accordingly, we corroborate that the accumulation of auxins stimulates elongation as a direct consequence of the upregulation of cell expansion genes, which is also in tune with experimental evidence (3).

**Physiological level**

As mentioned above, the ability of plants to describe curve trajectories relies on a differential growth in both sides of the elongating organ (planar projection) caused by a differential accumulation of auxins induced by the gravity action (Fig. 1 c) (26). For simplicity, we consider a linear distribution of auxins along the transversal axis. This distribution depends on the angle of the plant with respect to the vertical (\( \theta \)). When the plant is straight (\( \theta = 0 \)), the auxin distribution is symmetric. At maximal bending (\( \theta = \pi/2 \)), the ratio of auxins between the two sides of the plant organ is also maximal, and this ratio has been experimentally estimated to be at most double (3,4). By continuity, we assume that the total amount of auxins (\( x_{\text{tot}} \)) is constant, being

\[
x_{\text{down}}(\theta) = \frac{\zeta(1, \theta)x_{\text{tot}}}{x_{\text{up}}(\theta)} = \frac{\zeta(0, \theta)x_{\text{tot}}}{x_{\text{up}}(0)} = \frac{\zeta(\pi/2, \theta)x_{\text{tot}}}{x_{\text{up}}(\pi/2)} = \frac{\zeta(\theta)}{\zeta(0)}x_{\text{tot}},
\]

where \( \zeta(\theta) = \frac{\sin(\theta)}{\cos(\theta)} = r + (1 - 2r)(1/2 - \theta/\pi + 2\theta/\pi^2), \) is the minimum proportion of auxins in the upper flank (see Fig. S1 in the Supporting Material). The maximum auxin ratio is given by \( 1/\zeta_0 - 1 \). Hence, \( \nabla z(\theta) = z(x_{\text{down}}(\theta)) - z(x_{\text{up}}(0)) \).

As stated above, we consider that elongation is proportional to the level of expression of elongation genes at a given position (up or down) and orientation (\( \theta \)). Because this expression is modulated by the levels of auxins, and a change in the angle provokes a redistribution of auxins, the physiological response is time-coupled to the dynamics of the genetic circuit. Thus, by considering that the differential elongation provokes the curvature of the organ (2), the dynamics follows

\[
\frac{db}{dt} = \lambda \frac{\nabla z(\theta)}{D},
\]

where \( \lambda \) is the elongation rate relative to the expression of expansins, and \( D \) is the organ diameter. We also define

\[
\text{TABLE 1 Kinetic parameters (with typical values) used in this work}
\]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
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<tr>
<td>( \alpha )</td>
<td>Protein synthesis amount</td>
<td>400 mol*</td>
</tr>
<tr>
<td>( K )</td>
<td>ARF-DNA binding coefficient</td>
<td>10 mol*</td>
</tr>
<tr>
<td>( m )</td>
<td>Relative ARF-DNA binding affinity</td>
<td>10 mol*</td>
</tr>
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<td>( n )</td>
<td>Hill coefficient (ARF multimerization degree)</td>
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<td>( \rho )</td>
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</tr>
<tr>
<td>( \mu )</td>
<td>Heterodimerization equilibrium constant</td>
<td>10 mol^-1</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>Total ARF amount in the nucleus</td>
<td>100 mol</td>
</tr>
<tr>
<td>( \tau )</td>
<td>Relative stability of expansins over Aux/IAA proteins</td>
<td>3</td>
</tr>
<tr>
<td>( \Gamma_y )</td>
<td>Repression coefficient of DELLA on Aux/IAA proteins</td>
<td>1**</td>
</tr>
<tr>
<td>( \Gamma_z )</td>
<td>Repression coefficient of DELLA on expansins</td>
<td>1**</td>
</tr>
<tr>
<td>( \lambda )</td>
<td>Relative elongation rate</td>
<td>1 mm/(mol h)^1</td>
</tr>
<tr>
<td>( D )</td>
<td>Diameter of the elongating organ</td>
<td>1 mm**</td>
</tr>
<tr>
<td>( \zeta_0 )</td>
<td>Minimal proportion of auxins</td>
<td>0.33**</td>
</tr>
</tbody>
</table>

*Estimated from the amount of some nuclear proteins in yeast (22) given that Aux/IAA proteins are short-lived nuclear proteins (5).

1Estimated from the MAPK transcription factor Ste12 in yeast (23,24).

2Assuming that ARF dimers preferentially bind to Aux/IAA promoters (15).

3Based on quantification of homo- and heterodimers in HeLa cells (20).

4Estimated from the amount of the MAPK transcription factor Ste12 in yeast (22).

5Based on the kinetics of degradation of Aux/IAA proteins (21).

6**This work.

7Based on hypocotyl elongation in soybeans (25).

8Based on quantification of auxins under gravstimulation in Brassica oleracea (3) and peas (4).
a physiological dimensionless time $T = t\lambda /D$. We assume that the physiological timescale is greater than the molecular one, and hence the concentrations of the relevant molecules in the cell are considered to have reached their steady states. We use these values to compute the elongation and the corresponding degree of reorientation at each time step. Moreover, the diffusion of auxins and the protein synthesis are both sufficiently rapid to ensure decoupling of the timescales, which supports the assumption that the molecular system is in quasi-steady state. The diffusion coefficient of auxins is $\sim 10^{-3}$ mm$^2$/s (27); therefore, for a space of $\sim 1$ mm we have a diffusion time of $\sim 20$ min, which is on the order of the half-life of Aux/IAA proteins.

We then couple this physical description with the molecular model to simulate the gravitropic response. Given the possibility that the position of DELLA proteins in the regulatory circuit could lead to both a positive and a negative effect of gibberellins upon the gravitropic response, we investigated the dynamics of organ reorientation with our model under two hypothetical control strategies involving gibberellins: one ($S_1$) for low levels of DELLA with $\Gamma_g = 1$ and $\Gamma_z = 1$ (wild-type scenario, with normal levels of gibberellins), and one ($S_2$) for high levels of DELLA with $\Gamma_g = 0.5$ and $\Gamma_z = 0.75$ (with low levels of gibberellins). Accordingly, we simulated the dynamics of the organ reorientation under gravistimulation, where the plant is artificially rotated $90^\circ$ (Fig. 3). Of interest, our model predicts that the speed of the response would be higher in $S_2$ than in $S_1$. In fact, this discrepancy could be higher because DELLA proteins enhance the gradient of auxins by means of the activation of efflux carriers (28). Whereas the repression over expansins by DELLA ($\Gamma_x$) gives a monotonic effect, the repression over Aux/IAA ($\Gamma_y$) entails an optimal point in the reorientation ability (Fig. S2, Fig. S3, and Fig. S4), in agreement with Fig. 2 c. Also, the higher stability of expansins (or the higher degradation of Aux/IAA proteins) would allow a more rapid tropic response (Fig. S5).

In addition, we investigated the effect of the total amount of ARFs ($u_{tot}$). Our model predicts that multiple knockouts in some genes of the ARF family (18) would also cause a decrease in the speed of the response. In this way, genetic engineering could counteract deficient levels of gibberellins in the system. Of note, these predictions have been confirmed in parallel experimental work (9). Therefore, our model finely predicts the plant gravitropic response based on simple molecular interactions and allows the role of gibberellins (attenuation of the speed of reorientation) in such a response to be depicted.

**Integral control**

Similarly to mechanical and electronic systems, biological systems implement automatic control strategies to adjust their developmental behavior to the environment or to be robust under perturbations. This automatic control allows a system to continuously sense the output ($z$) and respond to the input ($x$) to maintain the reference state ($\theta_0 = 0$) (29). In control theory, a system is assumed to be in equilibrium and subjected to external perturbations that can alter the desired mode of operation. Control loops are designed to automatically correct such perturbations over the system. In this way, does the network of genetic interactions that govern the tropic plant response provide the expected robustness (16) in biological systems? This depends on the network topology and a proper parameterization ensuring the stability of the control system. At first sight, the network consists of a negative feedback loop, which has been demonstrated in other systems to be responsible for implementing an integral control (Fig. 4). This type of control uses the past trajectory to compute the deviation with respect to the reference value (steady state), and, in our case, perturbations at the auxin level could be counteracted (30).

To dissect the control structure and study its stability, we apply the Laplace transform ($\hat{\cdot}$ with domain variable $s$) to the system (Eq. 1) linearized around the steady state, to yield

$$\begin{align*}
(\phi + s)\hat{\Delta y} &= -y_0 \hat{\Delta x}, \\
(1/\tau + s)\hat{\Delta \hat{z}} &= \alpha \Gamma f_m'(y_0) \Delta \hat{y}.
\end{align*}$$

**FIGURE 3** Dynamic plant response in a simulated experiment under gravistimulation (plant artificially rotated $90^\circ$): (a) for two control strategies modulated by gibberellins ($S_1$ for low levels and $S_2$ for high levels of DELLA proteins), and (b) for different amounts of total ARF proteins ($u_{tot}$). The rest of the parameter values are shown in Table 1.

**FIGURE 4** Control diagram (negative feedback loop) implemented in plants for gravitropic response (Eq. 5). In this case, $\hat{\cdot}$ represents the Laplace transform, and $s$ is the corresponding domain variable.
where $\phi = 1 + x_0 - a_1 f'_1(y_0)$. The basic control scheme of a system consists of a sensor-controller that implements the negative feedback loop. In our case, the system consists of two subsystems (represented by the states of two proteins) and the sensory machinery is implemented by the plant through a spatial hormone gradient. Gravity modulates the level of auxins in both sides of the organ to lead to reorientation. Here, the system is of second order, whereas the global system is of third order due to the integral sensor control. Thus, the stability condition (necessary and sufficient) is reduced to $3.2.10^9 m^2 K^6 > \tau \alpha^3 u_{tot}^2$ (for details see Supporting Material). In the particular case of the parameters shown in Table 1, the stability condition is satisfied.

Hence, perturbations in the level of auxins are corrected to the system to the reference state. In addition, gibberellins modulate the magnitude of the response in such a way that the accumulation of DELLA proteins during the deficiency of gibberellins accelerates the corrective response. In fact, what gibberellins control is ultimately the transient effect exerted by gibberellins on such noise propagation. We further investigated noise propagation in single cells auxins. This raises the question: Can different levels of this topology and, in particular, how it affects expansin appear for stochastic events (31). Now, the system of differential equations accounting for molecular noise (intrinsic and extrinsic) reads as

$$
\frac{dy}{dt} = a_1 f_1(y) - xy - y + \xi_y(t) + \xi_x(t),
$$

$$
\frac{dz}{dt} = a_2 f_2(y) - \frac{1}{\tau} z + \xi_z(t) + \xi_y(t),
$$

where the stochastic processes $\xi_y(t)$ and $\xi_z(t)$ account for the intrinsic noise, and the common process $\xi_y(t)$ accounts for the extrinsic noise (see Supporting Material). According to previous experimental results (32), the autocorrelation time for the intrinsic noise is very small, and therefore we can assume that their statistics are $\langle \xi_y(t) \rangle = 0$ and $\langle \xi_y(t_0) \xi_y(t + t) \rangle = \tau^2 \delta(t)$ for $i = y, z$, where $\langle \cdot \rangle$ represents the ensemble average. However, the autocorrelation time for the extrinsic noise is on the order of the protein half-lives (32), so we assume $\langle \xi_y(t) \rangle = 0$ and $\langle \xi_y(t_0) \xi_y(t + t) \rangle = \tau^2 \delta(t)$. For auxins, we consider a distribution with $\langle x(t) \rangle = x_0$ and $\langle \Delta x(t) \Delta x(t + t) \rangle = x_0 q_x^2 \frac{1}{2\tau} e^{-|t|/\tau}$. Here, we take the approximation of mean field theory, assuming a perturbative regime, by which the dynamics is decomposed as $z(t) = z(t) + \Delta z(t)$, where the mean value is the deterministic solution $\langle z(t) \rangle = z_0$, and the perturbative term only depends on the mean field. Hence, we have $q_x^2 = 2y_0(1 + x_0)$ and $q_y^2 = 2x_0/\tau$. In addition, $q_y$ and $q_x$ are free parameters that control the amplitude of the auxin and extrinsic (global) noise.

We define noise as $\eta_y^2 = \Delta z^2 / z_0^2$, which we can analytically calculate by taking advantage of the previous considerations (details in Supporting Material). Introducing $A = -a_1 f'_1(y_0)$ gives

$$
\eta_y^2 = \frac{1 + x_0}{\phi y_0} + \frac{x_0}{2\phi(\tau \phi + 1)} q_x^2 + \frac{1}{2\phi(\tau \phi + 1)y_0} q_y^2,
$$

$$
\eta_z^2 = \frac{1}{z_0} + \frac{\tau A y_0^2}{2(\tau \phi + 1)z_0^2} \left( \frac{\tau (\tau \phi + 1)}{y_0} \right)^2 \eta_y^2 - \left( \frac{1 + x_0}{y_0} \right)^2 + \left( \frac{1}{2} - \frac{\tau A (\tau \phi + 1)}{(\tau \phi + 1)^2} \right) \frac{\tau^3}{2\tau^3} q_y^2.
$$

In essence, noise can be decomposed into three terms: one intrinsic to the gene (mostly Poisson-like), one due to propagation, and one extrinsic due to global effects that are common to all species (33). The stochasticity arises from a low number of molecules, which induces fluctuations in gene expression. To study noise propagation, we plot the noise in proteins for different amounts of auxins (Fig. 5). For negligible noise levels in auxins ($q_x = 0$), noise in expansins is mostly Poissonian in the absence of extrinsic sources, indicating that propagation events from upstream sources are not significant. In fact, in this case, the noise in expansins is basically inversely proportional to the noise in Aux/IAA proteins ($1/\eta_y^2 \propto \eta_z^2 x_0$). Because the level of auxins correlates positively with the expression of expansins, its noise will decrease with auxins, thus reducing the variability in the cells located in the lower side of the organ. However, for high noise levels in auxins ($q_y = 1$), there is a maximum in the noise in expansins at intermediate auxin.
amounts due to the trade-off between the intrinsic and propagation terms \((\eta^2_q \propto p(x_0)/x_0)\), being \(p\) a quadratic polynomial. This is interesting because small perturbations in the amount of auxins could lead to notable changes in noise in expansins. In addition, our model predicts that deficient levels of gibberellins (i.e., high levels of DELLA proteins) would entail a reduction of the noise in protein expression, which could reduce the variability in the physiological response of a population of gravitropically stimulated plants. Of note, this prediction of variability in the physiological response has been confirmed in parallel experimental work (9).

**DISCUSSION**

In this work, we have proposed a model based on nonlinear dynamics and stochastic modeling to show how plants have programmed an integral control by coupling transcription circuits with hormone signaling. Of importance, our molecular model integrates a novel (to our knowledge) regulatory interaction: repression of the expression of Aux/IAA proteins (encoding auxin-signaling elements) by DELLA proteins (which are gibberellin-signaling elements). This interaction has been shown to affect gravitropic reorientation in etiolated seedlings (9), and our model establishes that the mechanism relies on the generation of a negative feedback loop involving the two hormones that implements a system of integral control. Of interest, as in bacterial chemotaxis, such a control strategy is generally responsible for perfect adaptations by which the output of the system always reaches its operating point after a transient response when the input level is varied (30). Alternative modes to regulate the auxin level by other types of control, such as a proportional control, would not return the system to the reference state, because the output level in steady state is dependent on the input signal. On the other hand, an integro-differential control could provide a finer strategy because it would be able to anticipate the future of the signal. However, such a control is not applicable to real systems that are subjected to random fluctuations, because for a noisy signal the differential control stage would introduce an undesirable deviation.

It is known that hormones redundantly regulate gene expression during plant development. Cross talk between hormones has been generally depicted as occurring at the level of signal transduction, although more recent molecular evidence points to multiple integration points, including gene regulation (34,35). The circuit we have modeled here represents a mechanism in which signal transduction and gene regulation are intertwined, and in fact transcriptional regulation becomes an integral part of the feedback regulatory module that provides plasticity to the output trait.

Recently, Middleton et al. (17) developed a deterministic mathematical model of the regulatory feedback loop of auxins, but without coupling to a physical model of plant reorientation, to analyze the dynamical features of the system. Our model simplifies the underlying complexity to capture the essential elements at play in the gravitropic response, and it allows us to predict the physiological response under molecular changes. In addition to the role of gibberellins as modulators of auxin sensitivity, the analysis of our model highlights a previously unsuspected feature of the hormonal circuit that regulates gravitropic responses: the positive effect of gibberellins upon noise propagation. This occurs in such a way that gibberellins are able to decrease the response to gravity, and also increase the variance of this response. Both of these phenomena have been confirmed in vivo (9). Of interest, the increase in noise propagation represents an intrinsic property of the regulatory circuit studied here, and it is caused by the incorporation of high levels of gibberellins into the circuit. From this perspective, our analysis suggests for the first time, to our knowledge, a molecular basis for noise generation in the biological response to gravity.

Finally, one question that becomes relevant from a biological point of view is why nature has selected a molecular mechanism that attenuates the ability of plants to respond to gravity, which is an important environmental cue that determines growth orientation. In other words, what selective advantage is provided by this attenuation? In this particular case, one possibility is that the generation of variance in gravitropism allows individual plants to respond in a more precise way to light cues, such as when seedlings emerge from the soil or exhibit shade avoidance (36). In general,
our results suggest that partially redundant signaling pathways may impinge on each other not only to regulate the magnitude of the response, but also to maintain an elevated degree of plasticity from individual to individual (37).

SUPPORTING MATERIAL

Additional text, with equations, and five figures are available at http://www.biophysj.org/biophysj/supplemental/S0006-3495(11)00777-6.

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