Molecular noise can minimize the collective sensitivity of a clonal heterogeneous cell population

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Abstract

It is now widely accepted that molecular noise, rather than be always detrimental, introduces in many circumstances the required boost to reach fundamental cellular activities or strategies otherwise unattainable. In threshold-like genetic systems, molecular noise serves to generate heterogeneous responses in a clonal population, also in a tissue, due to cell-to-cell variability. Here, we derived a mathematical framework from which we could study in detail this effect. We focused on a minimal decision-making gene circuit implemented as a transcriptional positive-feedback loop. We evidenced that when the individual responses of each cell within the population are averaged, a sort of collective behavior, the resulting dose-response curve is linearized. In other words, the population is less sensitive than the individuals, which otherwise enhances the information transfer from signal to response. We found that the distance to the ideal linear response of the cell population is minimized for a particular noise level, and also characterized the interplay between intrinsic and extrinsic noise. Overall, our results highlight how cells could, by acting as a collective, entangle their genetic systems with their environments by adjusting the intracellular noise levels.

Synopsis

Isogenic populations can present large variability in gene expression from cell to cell. One important driver of this variability is molecular noise, i.e., stochastic fluctuations in the biochemical reactions required for gene expression. Here, we show that this variability can help to produce a population response, i.e., average gene expression level of every cell, that is linear. This has implications on how cell populations perform analog computations, or enhance fidelity when environmental signals are transduced.

Introduction

A heterogeneous response of a clonal cell population upon induction with a given signal molecule is widely observed in biology [1, 2, 3, 4, 5]. Certainly, what can be behind this heterogeneous response is an all-or-none genetic switch [6], as well as the inherent stochasticity of all biochemical reactions [7, 8], which makes that, within certain signaling levels, some cells go ON (target gene expressed), whilst others remain OFF (target gene unexpressed). In particular, biological systems integrate the effect of intrinsic and extrinsic sources

of molecular noise. How gene expression is influenced by these two types of noise has been the subject of extensive work over the last years [9, 10, 11, 12, 13]. These studies have shown, for instance, that intrinsic noise can be assumed as multiplicative white noise, whilst extrinsic noise tends to be considered as additive colored noise (with the correlation time equal to the cell cycle time) [10, 11]. They have also revealed the regimes where one source of noise dominates over the other [12], and further how different regulatory architectures determine particular levels of gene expression noise [14, 15, 16, 17], including how noise is propagated through those gene circuits [18].

However, what is less studied is how the average response of the clonal population is able to be sensitive to the signal molecule; in other words, how linear is the collective response. Here, we refer to this feature as *collective sensitivity* (Fig. 1). This aspect is important because it can be exploited to offer new applications in biology, such as the generation of analog computations [19]. Previous work has shown, for instance, that a negative-feedback loop is able to generate more linear responses [20, 21]. But this linearization occurs at the single-cell level, which causes homogeneous responses. Maintaining a heterogeneous response of

Figure 1: Scheme of a cell population induced by a signal. Two scenarios with equal collective response are shown; in one the population is homogeneous (graded response, labelled as 1), in the other heterogeneous (all-or-none response, labelled as 2).

a population can be very advantageous for diversifying survival strategies in fluctuating environments (e.g., a subset of cells ON to face sudden high-stress levels) [22, 23]. In this sense, a scenario combining, on one side, a variable response from cell to cell and, on the other, a graded response in terms of population would be intriguing (note that different individual and collective behaviors could be integrated [24]). Here, we will show how molecular noise is instrumental to this end.

In this work, we present a theoretical framework based on a simple stochastic differential equation, accounting for intrinsic and extrinsic noise, describing the dynamics of an inducible genetic switch displaying a bistable response (in particular, a positive-feedback loop). This circuit allows cells to respond to analog signals in a digital manner. We solved analytically this model thanks to the Fokker-Planck equation to obtain the probability distribution of gene expression, which we used to calculate the collective sensitivity, as well as the information transduction capacity [25, 26], of a clonal cell population for varying noise attributes.

Methods

Construction of a stochastic differential equation

We considered a biological system in which a signal molecule (x denotes its normalized concentration) activates the expression of a gene that codes for a regulatory protein (y denotes its normalized concentration). This protein can also regulate its own production. By following the Langevin approach [8], the stochastic differential equation that math-

ematically models the dynamics of gene expression reads

$$\frac{dy}{dt} = f(x, y) + q_i(x, y)\xi_i(t) + q_e(y)\xi_e(t), \quad (1)$$

where $f(x, y)$ accounts for the deterministic regulatory behavior, whilst ξ_i and ξ_e are two independent stochastic processes [$\langle \xi_i(t)\xi_e(t) \rangle = 0$]. Here, on one side, ξ_i models the source of intrinsic noise, and its statistics are $\langle \xi_i(t) \rangle = 0$ and $\langle \xi_i(0)\xi_i(t) \rangle = \delta(t)$ (white noise, i.e., without correlation between times, which leads to have a constant power spectrum). On the other, ξ_e models the source of extrinsic noise, and now the statistics are $\langle \xi_e(t) \rangle = 0$ and $\langle \xi_e(0)\xi_e(t) \rangle = \frac{1}{2\tau}e^{-t/\tau}$ (colored noise, i.e., with correlation between times, which leads to have a frequency-dependent power spectrum; τ is the correlation time). Moreover, q_i and q_e are, respectively, the intrinsic and extrinsic noise amplitudes (note that, as a general model, both q_i and q_e depend on the state of the system). Time was adequately rescaled by the effective turnover rate of the protein (this value depends on the cell growth rate and the protein degradation and maturation rates [27]). Note then that when the protein is stable $\tau = 1$, whilst $\tau > 1$ when the protein is short-lived.

Our minimal regulatory circuit is implemented by a gene autoactivating transcriptionally its own production [1]. This is a genetic implementation of a decision-making switch that, in the deterministic regime, becomes activated (ON) only if x is beyond a threshold, remaining otherwise in an unexpressed state (OFF) (Fig. 2a). The expression of the function $f(x, y)$ in Eq. (1) that models this switch reads

$$f(x, y) = \alpha_0 + \alpha \frac{y^n}{1 + y^n} - y + x, \quad (2)$$

where α_0 is the basal production rate, α the induced production rate, and n the degree of protein multimerization. Here, we used the following parameter values: $\alpha_0 = 0.01$, $\alpha = 2.5$, and $n = 2$. Note that the effect of the signal molecule is modeled here as a small perturbation over the system. According to this function, we identified four propensities. The intrinsic noise amplitude is then $q_i(x, y) = \sigma \sqrt{\alpha_0 + \alpha \frac{y^n}{1 + y^n} + y + x}$, where σ is a control parameter that modulates the number of molecules of the system [28].

The stationary solutions of the system in the deterministic regime depend on the x value. One solution can be approached by $\alpha_0 \simeq 0$ and the other by $(\alpha + \sqrt{\alpha^2 - 4})/2 \simeq \alpha$. Therefore, if x_0

denotes the threshold from which the system is induced (here, $x_0 = 10^{-3}$), and being θ the Heaviside function, the stationary solution can be written as $y \simeq \alpha\theta(x - x_0)$. The average value of the intrinsic noise amplitude, with a signal that fluctuates around the threshold, can be approached by $\langle q_i \rangle \simeq \sigma\sqrt{\alpha}$.

Re-formulation of the stochastic differential equation

Because our stochastic differential equation integrates two types of noise, we decided to re-formulate it to simplify the subsequent calculations. The stochastic process underlying extrinsic noise (ξ_e) can be explained in terms of a new independent stochastic process (ξ_j) with statistics $\langle \xi_j(t) \rangle = 0$ and $\langle \xi_j(0)\xi_j(t) \rangle = \delta(t)$ (i.e., white noise). Note that $\langle \xi_i(t)\xi_j(t) \rangle = 0$. By assuming an adiabatic process condition [29], we could state that

$$\frac{dy}{dt} \simeq \frac{f(x, y) + q_i(x, y)\xi_i(t) + q_e(y)\xi_j(t)}{1 - \tau\partial_y f(x, y) + \tau\frac{\partial_y q_e(y)}{q_e(y)}f(x, y)}. \quad (3)$$

For simplicity in the notation in the subsequent developments, we defined

$$f^*(x, y) = \frac{f(x, y)}{1 - \tau\partial_y f(x, y) + \tau\frac{\partial_y q_e(y)}{q_e(y)}f(x, y)} \quad (4)$$

and

$$q^*(x, y) = \frac{\sqrt{q_i(x, y)^2 + q_e(y)^2}}{1 - \tau\partial_y f(x, y) + \tau\frac{\partial_y q_e(y)}{q_e(y)}f(x, y)}. \quad (5)$$

Calculation of the stationary probability distribution of gene expression

To calculate the stationary probability distribution of y , we applied the Fokker-Planck equation over the resulting stochastic differential equation [30, 31]. This allows an analytical solution, avoiding the time-consuming stochastic simulation. For this calculation, x was considered constant. Thus, in the steady state we got

$$f^*(x, y)P(y|x) = \frac{1}{2}\partial_y[q^*(x, y)^2P(y|x)]. \quad (6)$$

The solution of this differential equation is

$$P(y|x) = \frac{C}{q^*(x, y)^2} e^{\int_0^y \frac{2f^*(x, s)}{q^*(x, s)^2} ds}, \quad (7)$$

where C is a normalization constant so that the total probability is 1.

Definition of signal variability

We considered that the concentration of the signal molecule is distributed normally in log scale around the threshold of the genetic switch. Precisely, the mean of this distribution is the threshold value (here, 10^{-3}), and the standard deviation $1/3$. Moreover, the distribution was considered bounded between $x_{min} = 10^{-4}$ and $x_{max} = 10^{-2}$ (i.e., one order of magnitude above/below the mean). We assumed that the cell population is initially not induced. At a given time it receives a signal (with value x), and then each cell within the population is assumed to produce a particular level of gene expression (with value y) depending on its intracellular noise levels. Here, we considered 10^5 realizations of the pair (x, y) .

Moreover, we here assumed slow signal fluctuations, i.e., the system has sufficient time to respond to those fluctuations. This is an important consideration because when signal fluctuations are rapid, molecular noise can turn a graded response into a threshold-like one [32].

Calculation of the distance to the linear response of a cell population

The collective response was considered as the average of the individual responses, i.e., $\langle y \rangle = \sum_i y_i$, with y_i the gene expression level of the i -th cell. The value of y_i corresponds to a realization using the probability distribution $P(y|x)$, for a given value of x . Thus, it can also be stated $\langle y \rangle = \int_0^\infty yP(y|x)dy$. In addition, being α_0 and $(\alpha + \sqrt{\alpha^2 - 4})/2$ the approximate stationary solutions of the system, the ideal linear response (y_{lin}) is given by

$$y_{lin}(x) \simeq \alpha_0 + \frac{\alpha + \sqrt{\alpha^2 - 4}}{2x_{max}}(x - x_{min}), \quad (8)$$

where the values of x_{min} and x_{max} are presented above. Hence, the (Euclidean) distance to the linear response (d) was calculated as

$$d = \int_{x_{min}}^{x_{max}} [\langle y(x) \rangle - y_{lin}(x)]^2 dx. \quad (9)$$

For numeric calculation, the input domain was discretized in 75 steps (in log scale). Then, shorter the distance, lower the collective sensitivity. However, large distances can indicate either threshold-like (for weak noise levels) or random (for strong noise levels) responses.

Figure 2: a) Scheme of the gene regulatory circuit considered here. The pervasive presence of molecular noise affecting gene expression makes that the single-cell response is all-or-none; but the cell-population response is graded. b) Representation of the distance to the linear response of a population (d) as a function of the intrinsic noise amplitude on average ($\langle q_i \rangle$). An optimal noise level is observed (labelled as A). In this plot, $q_e = 0$ (and also $\tau = 0$). c) Scatter plot (x, y) for $\langle q_i \rangle = 0.15$ (corresponding to the situation labelled as A in b), together with the average and ideal linear responses. An input window is presented to illustrate how the corresponding output response is.

Calculation of the information transfer at the population level

We used mutual information (I) to quantify how the population response is able to represent the signal, i.e., how information is transferred through the integration of gene regulation. This metric outperforms the correlation coefficient to evaluate input-output associations [33]. This was calculated as

$$I = \int_0^\infty \int_{x_{min}}^{x_{max}} P(x) P(\langle y \rangle | x) \log_2 \left(\frac{P(\langle y \rangle | x)}{P(\langle y \rangle)} \right) dx d\langle y \rangle. \quad (10)$$

Note that the integration is over the population response ($\langle y \rangle$; taken of 10^3 cells) and not over the single-cell response (y). For numeric calculation, the input and output domains were discretized in 100 steps (in linear scale; in the practice, $\langle y \rangle$ between 0 and α). In this case, the concentration of the signal molecule was considered distributed uniformly between x_{min} and x_{max} .

Results and discussion

Intrinsic noise linearizes the collective response

We considered a scenario where the same environmental stimulus is perceived by multiple cells conforming a population (or even a tissue). We considered that this stimulus is transduced into a signal molecule that operates intracellularly and that can activate the transcription of a genetic switch initially uninduced (Fig. 2a). Here, the switch is a bistable circuit, exhibiting a discontinuous transition (from OFF to ON) in the dose-response curve (i.e., threshold-like system). This generates an analog-to-digital behavior. In the deterministic regime, the switch is induced only when the concentration of the signal molecule is above the threshold. However, if the switch is noisy, there are noise-induced crossings, and then concentrations of the signal molecule below the threshold, for instance, can induce the switch [34]. The frequency of these crossings depends on the amount of noise (note that for very high noise lev-

els the system behaves randomly). This stochastic crossing is indeed responsible of generating a heterogeneous cell population [1].

At the same time, this can generate a linearization of the collective response (analog-to-analog behavior). Fig. 2c illustrates this effect. The average of the stochastic responses, mainly when the signal value is close to the threshold, produces intermediate output levels; levels that are not reached by output of a single cell. Moreover, an optimal level of linearization is expected due to the random behavior of the system for very high noise levels (leading to a flat dose-response curve in population). The simulation of our mathematical model confirms the existence of a minimum in collective sensitivity when intrinsic noise is assumed (Fig. 2b; $d_{min} = 1.8$ for $\langle q_i \rangle = 0.15$). Arguably, it is the multiplicative effect of this noise what gives rise to this phenomenon (i.e., larger fluctuations for higher gene expression levels). A dose-response curve more linear also contributes, at the population level, to process information with lesser loss from the environment (see below) [20, 35].

Therefore, it could be beneficial for cells living in a population to adjust their intracellular noise levels. Intrinsic noise can be adjusted by varying the number of protein molecules implementing the circuit [10]. This can be accomplished, for instance, by reducing the binding affinity between the transcription factor and the DNA promoter (i.e., tighter regulation), or by using a protein degradation tag. Intrinsic noise can also be adjusted by tuning the balance between transcription and translation rates, maintaining the same protein production [2, 8].

Extrinsic noise also produces a linearization effect

We then analyzed the effect of extrinsic noise in a scenario of mixed noises (Fig. 3a). First, we considered the extrinsic noise amplitude as additive (i.e., q_e constant). This models fluctuations in the cellular machinery (e.g., in the number of available RNA polymerases for transcription) that are decoupled from the gene expression of the system. By simulating our mathematical model, we saw that the distance to the ideal linear response (d) increases from 1.8 to 6 when a small amount of extrinsic noise is added to a system with an optimal intrinsic noise level ($\langle q_i \rangle = 0.15$). We then wondered if the addition of more extrinsic noise could revert this situation. Indeed, we found that in this scenario of mixed noises there is also an

optimal level of extrinsic noise so that the collective sensitivity is minimal (Fig. 3b; $d_{min} = 2.1$ for $q_e = 0.02$). However, in this case the linearization of the collective response is less good, as shown in Fig. 3c. We argue that the additive effect of extrinsic noise is what contributes to this suboptimal behavior of the population.

Second, we analyzed the effect of extrinsic noise when it is multiplicative (i.e., q_e variable), now assessing two different values of the correlation time of these fluctuations (τ). For that, we just considered q_e proportional to y (i.e., $q_e = \gamma y$, with γ a constant that can vary to set different noise levels). This models an interplay between the cellular machinery and the state of the system. In this case, the average value of the extrinsic noise amplitude can be approached by $\langle q_e \rangle \simeq \gamma \alpha / 2$. Again, we started by adding a small amount of extrinsic noise to a system with an optimal intrinsic noise level. We saw that d increases with this addition, but much more for $\tau = 1$ than for $\tau = 0.1$. This is because the colored fluctuations are reduced to white ones in the limit $\tau \rightarrow 0$, and then the disarrange in linearization due to additional noise is higher in case of $\tau = 1$ (note that this is the actual case). Here, we also found an optimal level of extrinsic noise to make more linear the dose-response curve in population (Fig. 3d; $d_{min} = 1.1$ for $\langle q_e \rangle = 0.12$ in case of $\tau = 1$; similar results were obtained for $\tau > 1$). In case of $\tau = 0.1$, the minimum is shifted towards lower values of noise ($d_{min} = 1.1$ for $\langle q_e \rangle = 0.04$). Note however that in these two cases with multiplicative amplitude the linearization of the collective response is better (Figs. 3e, 3f).

Values of extrinsic noise amplitude of about 10% of the average gene expression levels, as the ones obtained here to minimize d , seem low in bacteria [36]. In this regard, cells that limit the extrinsic noise levels appear suitable to conform a population with analog behavior. For that, both environmental and genetic factors make significant contributions. First, cells should live in rich environments, which allow deploying metabolisms where the amount of cellular resources, such as RNA polymerases or ribosomes, are abundant [10]. Second, if the switch only receives the signal to elicit the response and works not influenced by further regulations to maintain a given expression level (i.e., if it works in isolation), the effect of extrinsic noise will be limited [37]. Yet, this study could be refined with the decomposition of the different sources of extrinsic noise [38].

Figure 3: a) Gene expression is broadly affected by two sources of noise: intrinsic and extrinsic. b) Representation of the distance to the linear response of a population (d) as a function of the extrinsic noise amplitude (q_e) when it is assumed additive. In this plot, $\langle q_i \rangle = 0.15$ and $\tau = 1$. An optimal noise level is observed (labelled as A). c) Scatter plot (x, y) for $q_e = 0.02$ (corresponding to the situation labelled as A in b), together with the average and ideal linear responses. An input window is presented to illustrate how the corresponding output response is. d) Representation of the distance (d) as a function of the extrinsic noise amplitude on average ($\langle q_e \rangle$) when it is assumed multiplicative. In this plot, $\langle q_i \rangle = 0.15$ and $\tau = 1$ or $\tau = 0.1$. For each value of τ an optimal noise level is observed (labelled as B and C). e, f) Scatter plots (x, y) for $\langle q_e \rangle = 0.04$ (corresponding to the situation labelled as B in d) and $\langle q_e \rangle = 0.12$ (situation labelled as C in d), together with the average and ideal linear responses. The input windows are also presented, and the labels shown in c also apply here.

The balance between intrinsic and extrinsic noise helps the collective to get better information

We finally studied how information is transmitted at the population level. For that, we considered that each cell represents a channel through which information can circulate [26]. Then, a cell population represents multiple channels in parallel. First, Fig. 4a shows the optimal balance between the amplitudes of intrinsic and extrinsic noise (considering both multiplicative) to reach a minimal d . Essentially, the higher the intrinsic noise, the higher should be the extrinsic noise. This suggests that cells could coordinate both types of noise to minimize the collective sensitivity. Second, that the dose-response curve is close to the ideal linear response entails a better information transfer (from x to y). This means that the entire range of signaling (i.e., signal molecule concentrations) maps to the entire range of possible responses (i.e., gene expression levels). In other words, the distributions of signals and responses are similar. This has been experimentally measured in case of a negative-feedback loop in yeast [20]. In terms of the collective, this means that there are always two different subpopulations (ON/OFF) in the medium, whose ratio is given by the input signal value; a potential advantageous scenario in case of fluctuating environments [22, 23]. In Fig. 4b we show the collective responses for three different balances of intrinsic and extrinsic noise, being one optimal (to minimize d). As expected, mutual information is higher for the optimal balance ($I_{max} = 4.38$ for $\langle q_i \rangle = 0.13$ and $\langle q_e \rangle = 0.1$) than for the other cases.

A fine combination of theoretical and experimental analyses of tumor necrosis factor signaling in mouse cells revealed that information transfer scales with the logarithm of the product of the number of cells in the population and the signal-to-noise ratio (i.e., the square of the dynamic range of input signal over the amplitude of noise) [26]. But this relationship holds for a linear model between y and x (leading to homogeneity). Arguably, the uncertainty of each cellular response is balanced by the population (the larger the population, the more accurate the balance), and noise is detrimental to transmit information in this case (the higher the noise, the lower the signal-to-noise ratio). However, for a highly nonlinear model between y and x (leading to heterogeneity), the effect of noise can be beneficial, as we here show (again better fidelity for a larger population). Indeed,

the existence of an optimal signal-to-noise ratio in case of multiple information channels working in parallel is a phenomenon known as suprathreshold stochastic resonance [39]. In addition, as well as different genetic networks influence information processing [20, 26], cellular networks also do. Indeed, the gain in information here reported is due to the independent processing of each cell within the population. This way, intercellular signaling mechanisms (e.g., quorum sensing in bacteria [40]) can be detrimental in this case if they homogenize the output responses.

For a gene with autoactivation, monostability is a regime more advantageous for information transmission than bistability at the single-cell level [35]. In this regard, the system could easily enter into this regime by reducing the production rate (α) if needed. Our results highlight that, in a regime of bistability, information transmission is enhanced when it is looked at the population level, which provides a new view of the autoactivation motif. Taken together, these results have implications on how cell populations extract information from the environments where they live.

Conclusion

Living cells can adjust the underlying gene regulatory architectures in order to reduce or exploit molecular noise [14, 15, 16, 17]. For example, negative feedbacks serve to reduce noise in gene expression, whilst positive feedbacks are generally drivers of variability (with the emergence of subpopulations even without bistability [4]). In the latter case (i.e., threshold-like genetic systems), noisy gene expression can be exploited collectively. A proper balance between intrinsic and extrinsic noise appears instrumental to produce more linear responses in terms of cell population (analog behavior) [34]. In the limit, this ensures that any environmental change is perceived by the population (by shifting the ratio of the subpopulations), i.e., that the population processes a high amount of information from the environment. For that, cells must read the same signal, operate independently, and aggregate the resulting responses [26].

In sum, our results indicate that the mechanisms that modulate the different sources of noise have fundamental implications for assessing both naturally-evolved or rationally-engineered systems that make reliable decisions in biology.

Figure 4: a) Optimal relationship between the intrinsic and extrinsic noise amplitudes on average ($\langle q_i \rangle$ and $\langle q_e \rangle$); note that both noises are considered multiplicative. This corresponds to the minimal distance of the actual response to the ideal linear response of a population. Three situations are labelled as A ($\langle q_i \rangle = 0.13$ and $\langle q_e \rangle = 0.1$; optimal), B ($\langle q_i \rangle = 1$ and $\langle q_e \rangle = 0.1$), and C ($\langle q_i \rangle = 0.03$ and $\langle q_e \rangle = 0.1$). b) Scatter plot (x, y) for these three situations, showing that the situation labelled as A (the one with optimal balance intrinsic/extrinsic noise) produces a response that is closer to the ideal linear response (dashed line). The calculated values of mutual information from the signal to the collective response (I) are shown.

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