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Modeling the genome-wide transient response to stimuli in yeast: adaptation through integral feedback

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Abstract— **The gene expression response of yeast to various types of stresses/perturbations shows a common pattern for the vast majority of genes, characterized by a quick transient peak followed by a return to the basal level (adaptation). In order to model this transient and the consequent adaptation, we use the idea of integral feedback (the integral representing the relative concentration of gene products). The resulting linear system with input explain sufficiently well the different time constants observable in the transient response while, at the same time, being in agreement with the known experimental degradation rates measurements.**

I. Introduction

Typically, at the level of gene expression, the response to a stimulus, or to a change in some environmental condition, or even to the substrate composition can be decomposed into a rapid adaptation phase [1], [2], [3], [4], [5] possibly superimposed to a long term permanent modification of the gene expression "steady state" (happening, for example, at the diauxic shift, [6]). We are interested here only in the first phenomenon, occurring with a typical time constant of the order of the tens of minutes. For *S.cerevisiae*, the rapid adaptation described in [3], [7], [1], [5] consists essentially of a transient change in the mRNA concentration followed by a return to the basal pre-stimulus level for almost the whole population of genes. This adaptation phenomenon is observed in response to both temporary stimuli (such as the nutrient somministration of [5]) and to permanent ones (such as the environmental stresses of [3]). A simple correlation analysis reveals that the responses to different types of stimuli have consistent similarities and are strongly correlated with the Half Life (HL) of the corresponding genes.

The aim of this paper is to propose a dynamical model for the genome-wide rapid adaptation of the transient response to stimuli able to explain the following features:

- robust adaptation to stimuli of various "order" i.e., both vanishing and persistent stimuli are reabsorbed;
- the rise time of the transient peak is shorter than its decay time (i.e., time needed to return to basal level). This last is of the same magnitude as the degradation time constant (HL) of the genes inferred from experimental data [8], [9], [10];
- the transient response typically does not induce oscillations (noticeable above the noise level);
- both the maximal amplitude of the transient peak and the area under the transient response are roughly proportional to the HL of the genes, while instead the peaking time (i.e., instant at which a gene has its maximal excursion during the transient) is not significantly correlated with HL.

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Adaptation, intended as the mechanism by means of which a biological system is able to recover the "best" working level of a variable in spite of a persistent stimulus, is common to many biological systems. Examples are numerous: various signal transduction pathways [11], bacterial chemotaxis [12] sensory transduction [13]. Following the intuition of [14], a control-theoretic interpretation of adaptation is in terms of a "purely" integral feedback loop. In this scheme, the integral of the displacement from a nominal level (i.e., the error) of a variable is fed back with negative sign. Adaptation is achieved as this variable returns to the nominal level (error $\rightarrow$ 0) in spite of a persistent stimulus (that would otherwise alter the steady state value, in absence of feedback). In the context of the present paper, the variable being integrated is the relative mRNA abundance, and its integral represents the relative abundance of the corresponding gene product. The cells work best when both genes and proteins are at a nominal level and adaptation reflects the attempt to maintain this condition in spite of external stimuli (not inducing dramatic changes in the cells functionality). Such a negative feedback, called "autogenous control", was introduced more than 30 years ago [15], [16] to model gene negative autoregulation. Among its dynamical features, it allows to reduce fluctuations around the steady state [17] and to decrease the rise time of a response [18]. As typically protein turnover rates are longer than their mRNA counterparts [19], in the time scale of interest changes in mRNA concentration reflect into a change of equal sign in the concentration of the corresponding proteins. We assume here that this quantity (the integral mentioned above) acts on the mRNA transcription rate in order to reequilibrate the gene expression to the nominal level of concentration.

The simplest possible model representing adaptation through integral feedback corresponds for each gene to a bidimensional linear system with input. The requirements above can all be satisfied very naturally by choosing the modes (eigenvalues) of the system and the sign of the input response. For example, the time constants of the rising and decay fronts of the transient response yield a fast mode and a slow mode, and this last must be comparable with the mRNA turnover rate. As the eigenvalues have different

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time constants, this already excludes the case of damped oscillations (eigenvalues must be real).

The whole process of "reequilibration" of the gene expression level to its pre-stimulus value is carried out in a highly coordinated manner: the pattern of up/down regulated functional categories is substantially faithful in the responses to different stimuli. Actually we not only can observe a strong degree of correlation among various stimuli having inhibitory effects (such as thermal, oxidative, osmotic stresses), but also anticorrelation between these and the stimuli having excitatory effects (such as the nutrient inputs of [5]). Overall this common pattern of expression reflects the values of HL assignable to the various functional categories and also the chain of events constituting the gene expression program of a cell: in an axis going from downregulation to upregulation for inhibitory stimuli (vice versa for activatory) we find "transcription" categories followed by "protein synthesis", "metabolism" and "protein degradation".

II. Model construction

All experiments we analyze consist of two-channel microarrays in which the mRNA abundance during the transient is hybridized against a basal pre-stimulus mRNA abundance thereby obtaining as measurement only a relative mRNA concentration for each gene. Returning to the pre-existing steady state corresponds to a value approaching 1 (or 0 if a log scale is considered as in Fig. 1).

As can be seen from Fig. 1, in each of the 5 time series of [3] considered, we observed that almost 90% of the genes have settled within an interval $[-\log_2(1.5), \log_2(1.5)]$ from the basal level (0 in the log scale considered) at the end of each transient (percentages go up to 95% if we consider an interval of $[-1, 1]$), while during the transient only $\sim 50\%$ of the genes remain inside the interval $[-1, 1]$ on each time series. Hence we can assume that the system undergoes a transient excursion in response to each stimulus, excursion which is reabsorbed in a time scale of the order of the tens of minutes.

The models for the transcriptional kinetics often describe the changes in mRNA concentration in terms of an activator/repressor transcription factor. Let m_i be the mRNA concentration relative to the basal level $m_i = \frac{[\text{mRNA}]_i^{\text{red}}}{[\text{mRNA}]_i^{\text{green}}}$ where the "red" and "green" channels are conventionally associated to the stimulus response and the basal mRNA level for the i-th gene. Letting δ_i be the degradation rate, then

$$\frac{dm_i}{dt} = -\delta_i m_i + f_i \tag{1}$$

where the function f_i describing the transcription rate is typically zero-order in m_i and can obey various types of dependence from the transcription factor(s) A_i, i.e., $f_i(A_i)$ can be linear, Michaelis-Menten or of Hill type [20], [21], [22], [5], [2], [23]. Applying any of these formulæ requires the knowledge of the transcription factor A_i acting on each gene. Even if this information is partially available for *S.cerevisiae*, predicting the kinetics of the transient response from them is troublesome for a number of reasons:

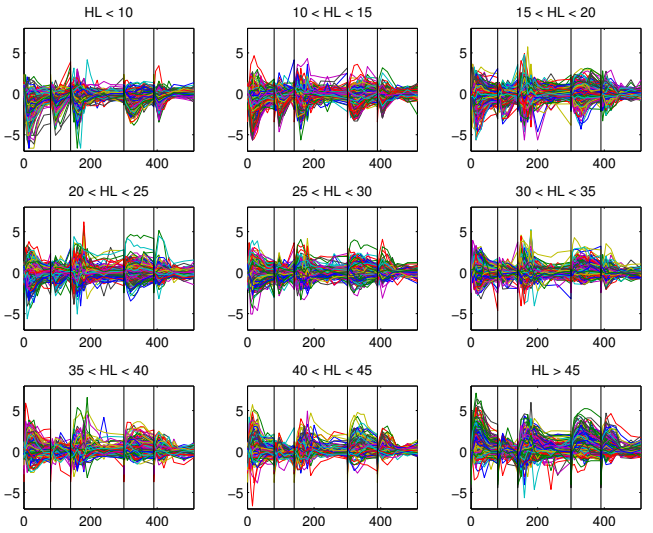

Fig. 1. Five time series from [3] showing the "step response" to different environmental stresses are shown (from left to right: heat shock, heat shock, hydrogen peroxide, sulfhydryl oxidizing agent, hyper-osmotic shock). For visualization purposes, the 5 series are shown sequentially one after the other. The time axis is in minutes, the relative mRNA abundance is in log_2 basis. In the 8 panels, the 5153 genes are ordered according to the respective HL (increasing from left to right, from top to bottom). In all 5 responses the trend followed during the transient is highly correlated, i.e. genes with similar HL behave similarly in the different step responses. In particular, genes with short HL tend to be downregulated while genes with larger HL upregulated.

- little is known on how the mRNA abundance influences dynamically the concentration of the corresponding gene product, even less on how and when the synthetized proteins are available for acting as transcription factors and thereby influencing the transcription (feedback mechanism);
- in the literature, the kinetic models mentioned above are mostly used for describing variations in the steady state following a perturbation, not for describing the dynamics itself;
- in terms of gene expression alone, the correlation between transcription factors and target genes is insignificant for the time series considered;
- the map transcription factors - target genes, though incomplete, is already combinatorially complex. In addition, its activation is known to be condition specific [24], and the sign of the interactions (activator/repressor) is often unavailable.

On top of all these complications, modeling the effect of an external stimulus u on the transcriptional regulation means expressing A_i as a function of u. As nothing is known about this further functional dependence $A_i = A_i(u)$, we decided to include in the model of the transcription rate f_i only a basal (constant) term plus a term linear in the stimulus u, of the form of a zero order kinetics in m_i:

$$\frac{dm_i}{dt} = -\delta_i m_i + c_i + b_i u. \tag{2}$$

The parameter c_i corresponds to the basal rate of transcrip-

tion in absence of external stimuli ($u = 0$). Therefore, since for the unperturbed steady state it must be $\bar{m}_i = c_i/\delta_i = 1$, we have $c_i = \delta_i$. The parameter b_i instead carries information about the activator/inhibitor effect of u on the mRNA concentration. When u is a persistent stimulus, e.g. $u(t) = 1$, $t \geqslant 0$, then in (2) the steady state value is modified to $m_i = (c_i + b_i u)/\delta_i = 1 + b_i u/\delta_i \neq 1$, i.e., the system (2) is not adapted to step-like inputs u and cannot recover its pre-stimulus mRNA level.

An increase in the transcription rate of the i-th gene induces an increase in the total quantity of mRNA produced over time

$$p_i(t) - \bar{p}_i = r \int_0^t (m_i(\tau) - \bar{m}_i) d\tau = r \int_0^t (m_i(\tau) - 1) d\tau \quad (3)$$

where, as above, $\bar{m}_i = 1$ is the pre-stimulus relative mRNA abundance, r is a rate constant (representing for example the ribosome density, and assumed to be the same for all genes) and $\bar{p}_i$ is an integration constant (representing the basal level of protein synthesis, see below). Differentiating this expression,

$$\frac{dp_i}{dt} = r(m_i - 1),$$

we see that p_i, up to a degradation term (at least of the same order of the HL if not slower, see [19]), describes the concentration of the corresponding gene product relative to the basal level, hereafter fixed as $\bar{p}_i = 1$. As the transcriptional perturbation propagates through the protein synthesis process with a time delay (e.g. diffusion-mediated, or due to the crossing of the nuclear envelope barrier), the influence of the protein degradation term on the dynamics becomes negligible for the time horizon of interest here.

Expanding on the concept of autogenous control, the main assumption we make in this paper is that an increase of the abundance of a certain protein well above (resp. below) the normal "working" level disfavors (resp. favors) the transcription of the corresponding gene. On the model this can be translated into an extra term exerting a negative feedback on m_i. Since this feedback effect acts in correspondence of a displacement from the basal level (i.e., for $p_i \neq 1$), we obtain the system of two paired equations:

$$\begin{aligned} \frac{dm_i}{dt} &= -\delta_i(m_i - 1) - a_i(p_i - 1) + b_i u \\ \frac{dp_i}{dt} &= r(m_i - 1) \end{aligned} \quad (4)$$

As can be seen from (3), the second equation in (4) represents an integral term which, when fed back with negative sign, has the effect of achieving perfect adaptation in m_i, allowing the mRNA abundance to return to its basal level in spite of a persistent stimulus u. The model predicts that the equilibrium is reached for p_i corresponding to $\tilde{p}_i = 1 + b/a$. In order to have $\tilde{p}_i > 0$, the parameters must therefore satisfy the consistency condition $b_i > -a_i$. De facto, the amplitude of p_i depends on the rate constant r. A value of r can be estimated from the data. Consider the time series of gene expression and compute (by numerical integration) the area under each expression profile using a formula like (3). For a gene experiencing no perturbation $m_i(t) = \bar{m}_i = 1$, hence $p_i(t) = \bar{p}_i = 1$ for all t. For a downregulated gene $m_i(t) < \bar{m}_i$, implying $p_i(t) - \bar{p}_i < 0$. As $p_i(t)$ is a relative concentration, we require $p_i(t) \geqslant 0$ for all t. This condition gives an upper bound for the value of r. Call $\mu = \max \left| \int_0^t (m_i(\tau) - 1) d\tau \right|$ for all genes for which $\int_0^t (m_i(\tau) - 1) d\tau < 0$ ("dowregulated"). Then $p_i(t) \geqslant 0$ is satisfied provided $1 - r\mu \geqslant 0$ i.e., $r < 1/\mu$. For all time series considered, a choice of $r = 0.01$ (motivated by the experimental data rather than by the dynamical model chosen) is sufficient to have biologically consistent values of $\tilde{p}_i$ for the range of a_i, b_i required by the fitting procedure.

As the model misses a degradation term in p_i, the protein concentration changes in response to the persistent stimulus from $\bar{p}_i$ to $\tilde{p}_i$ without ever returning to the basal level.

III. Model identification and analysis

To simplify calculations, it is convenient to change variables shifting the steady state (basal level) to the origin. Letting $x_i = \begin{bmatrix} m_i - 1 \\ p_i - 1 \end{bmatrix}$, $A_i = \begin{bmatrix} -\delta_i & -a_i \\ r & 0 \end{bmatrix}$, and $B_i = \begin{bmatrix} b_i \\ 0 \end{bmatrix}$, then for each gene we have the linear system (with input)

$$\dot{x}_i = A_i x_i + B_i u \quad (5)$$

whose solution is

$$x_i(t) = e^{A_i t} x_i(0) + \int_0^t e^{A_i(t-\tau)} B_i u(\tau) d\tau. \quad (6)$$

Since $\mathrm{tr}(A_i) = -\delta_i < 0$ and $\det(A_i) = r a_i > 0$, the system is always stable and its eigenvalues are:

$$s_{i,1,2} = -\frac{\delta_i}{2} \pm \frac{\gamma_i}{2}$$

where $\gamma_i = \sqrt{\delta_i^2 - 4 r a_i}$. A visual inspection of the time series shows that for the vast majority of genes the large excursion corresponding to the transient is damped without inducing oscillatory behavior (at least above what can be considered measurement noise). Hence in the model fitting we can assume:

1) the two eigenvalues are real, i.e., $\delta_i^2 - 4 r a_i > 0$;
2) the time constant of the fastest eigenvalue must be shorter than that of the "free degradation" given by the HL alone.

The two conditions are compatible with each other and with the model structure. In order to agree also with the available HL measures, we shall assume the following:

$$s_{i,1} < s_{i,2} \sim -\frac{\ln(2)}{\mathrm{HL}_i} < 0.$$

For example if we choose $s_{i,2} = -\frac{\ln(2)}{\mathrm{HL}_i}$, then we obtain the following conditions:

$$\begin{cases} a_i = -s_{i,2}(\delta_i + s_{i,2})/r > 0 \\ \delta_i > -2 s_{i,2} > 0 \end{cases} \quad (7)$$

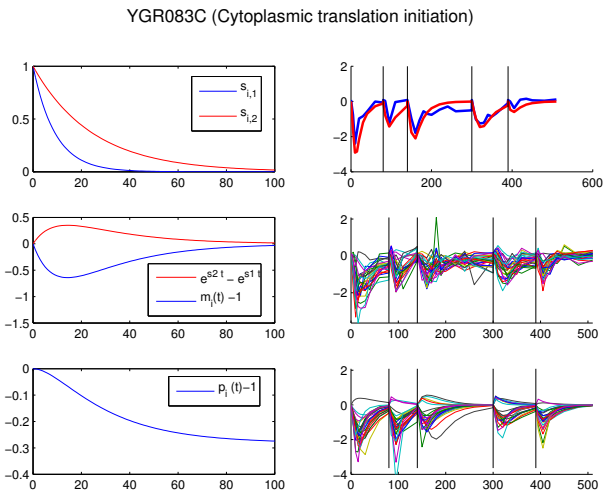

Fig. 2. Time response of the system in (5) to a step-like input, when $b_i < 0$ for the gene GCD2/YGR083C (subunit of the translation initiation factor eIF2B). Since the two modes have different real parts ($s_{i,1} = -0.11 < s_{i,2} = -0.04$ implies that $e^{s_{i,1}t}$ decays faster than $e^{s_{i,2}t}$, see top left plot), their difference typically shows a profile like that reproduced in the middle left plot. The sign of b_i then decides whether the gene is classified as up- or down-regulated by the stimuli (still middle plot). The area under the $m_i(t)$ time course, shown in the bottom left plot is monotonically growing. For the gene considered here, the experimental and reconstructed profiles are shown in the top right panel (blue and red respectively, both in $\log_2$ scale). If we look at the entire category of cytoplasmic transcription initiation, all profiles and their model-based reconstructions are shown in the middle and bottom plots of the right column.

where δ_i is the free parameter (together with b_i) for the data fitting. While the fastest mode $s_{i,1}$ is the one dominating the rising front of the transient response, in the setting in which HL are computed ("pure" degradation, with transcription blocked i.e., $c_i = 0$ in (2) and $a_i = 0$) only the slowest mode $s_{i,2}$ matters.

In correspondence of a persistent stimulus, $u(t) = 1$ for $t \geqslant 0$, the system (6) can be solved explicitly. Since at $t = 0$ the system is at rest (i.e., in the basal state $x_i(0) = [0\ 0]^T$ for all i, corresponding to $m_i(0) = 1$ and $p_i(0) = 1$), only the forced evolution (second term in (6)) matters and we obtain:

$$x_i(t) = \begin{bmatrix} m_i(t) - 1 \\ p_i(t) - 1 \end{bmatrix} = \frac{b_i}{\gamma_i} \begin{bmatrix} e^{s_{i,2}t} - e^{s_{i,1}t} \\ r\left(\frac{e^{s_{i,2}t}-1}{s_{i,2}} - \frac{e^{s_{i,1}t}-1}{s_{i,1}} \right) \end{bmatrix}. \quad (8)$$

Notice that as $t \to \infty$ from the second equation of (8) we obtain that $p_i(t) > 0$ if $rb_i \left(1/s_{i,1} - 1/s_{i,2}\right)/\gamma_i > -1$, i.e., for $b_i > -a_i$ as mentioned above.

The first equation of (8) can be used to fit the parameters in the dynamical model (5). For each gene, this corresponds to identify the values of δ_i and b_i that optimize the fit of $m_i(t)$ to the experimental time series. With these parameters, (5) is completely determined. The second equation of (8) can then be used to compare the area predicted by the model with the area computed from the experimental data.

A typical time course for $m_i(t)$ is shown in Fig. 2 for a stress-inhibited gene. The difference in the two eigenvalues $s_{i,1}$ and $s_{i,2}$ induces a transient response as shown in the left column of Fig. 2. In particular, since $s_{i,1} < s_{i,2}$, from the first equation of (8) we have a faster rising front (due to $s_{i,1}$) followed by a decay to the pre-stimulus level which resembles a typical first order degradation. Although the experimental condition is different from the mRNA turnover fitting experiments of [8], [9], [10] (where transcription is blocked), the time constants are indeed similar, thereby justifying our choice of $s_{i,2}$.

In the case of real eigenvalues, the lack of oscillatory behavior implies that $p_i(t)$ is typically monotonic, as can be checked by a direct numerical integration of the $m_i(t)$ profiles using (3). Hence for each response the area measured under the $m_i(t)$ profile corresponds to $p_i(t_{\text{end}})$. To reduce the effect of measurement noise, it is convenient to lump together genes whose products form a protein complex (PC). In fact these genes are known to have similar dynamics [10], observation largely confirmed by the time series under study. Sorting the PC complexes by the corresponding areas under the $m_i(t)$, see Fig. 3, is enlightening also from a biological point of view: the downregulated categories (negative areas in the log scale of Fig. 3) are essentially all involved into transcriptional and translational processes, while in the most upregulated categories are the respiratory chain complexes and the protein degradation machinery. Notice that, coherently, also the ribosomes biogenesis is very different between the cytoplasmic and mitochondrial compartments. For the PC complexes shown in Fig. 3, the comparison between numerically computed areas and model-based estimated areas (p_i) is shown in Fig. 5 (values are averaged over all genes forming the complex).

From Fig. 4, the fastest mode of A_i (dominating the rising front of the transient) is often much higher than the slowest mode (dominating the decaying front): $s_{i,1} \ll s_{i,2} < 0$. This last mode by assumption is chosen as the degradation rate constant. Since the mean HL is $\approx 25 \pm 15$ min, in the time horizon of the 5 series ($t_{\text{end}} = 80$, 60, 160, 90, 120 min for the 5 time courses), the transient has sufficient time to decay back at almost basal level for most genes. Therefore from (8) we can write the following relation:

$$p_i(t_{\text{end}}) - 1 \simeq \frac{b_i r}{\gamma_i}\left(\frac{1}{s_{i,1}} - \frac{1}{s_{i,2}}\right) \simeq -\frac{b_i r}{\gamma_i s_{i,2}} = \frac{b_i r}{\gamma_i}\text{HL}_i$$

This expression provides an explanation in terms of the model (5) of the roughly direct proportionality observed between area (computed from the data) and the values of HL, shown in Fig. 5 for the PC of Fig. 3. Notice on the same Fig. 5 the tight relationship between the amplitude (i.e., the signed peak in m_i) and the area (computed either via the model or from the data). From (8), model-based area and amplitude share the same gene-specific multiplicative constant b_i/γ_i.

For all 5 responses, the time at which the transient gene expression peaks, t_{peak}, is approximately 25 min. If $t_{\text{peak}} \sim$ 25min, then $e^{s_{i,1}t_{\text{peak}}} < 0.2$ for 87% of the genes (while $e^{s_{i,2}t_{\text{peak}}} < 0.2$ for only 7%) meaning that indeed the transient response declines due to the exhaustion of the fast mode.

IV. Comparing different input responses

For the 5 time series of Fig. 1, the similarities are much more consistent than the stimulus-specific differences. This can be deduced from the sign concordances of the b_i fitting. In Fig. 4 (bottom left panel) more than 50% of the 5153 genes have unanimous sign assignements in the 5 series ($\sim$ 80% have 4 sign concordances out of the 5 possible). These percentages increase considerably if we disregard low-variance genes. If the 5 time series are compared with 4 others from [7] also representing responses to prolonged stimuli (exposure to high Ca^{2+} and Na^{2+} and combinations of these with the immunosuppressive drug FK506) the pattern of up/down regulation is very similar. For the same PC as above the comparison of average areas is shown in Fig. 6, upper left. In [5] instead, the yeast culture is fed with pulses of glucose of different magnitude. In this case the sign of the responses is inverted for most genes, as can be seen in the two remaining scatter plots of Fig. 6.

V. Conclusions

Yeast reacts to a change of environmental conditions by means of a highly coordinated response which is faster than it would be expected from the "natural" degradation time constant. In this paper we propose a model able to explain this quick response by means of a feedback mechanism aiming at adapting the system to the new condition. From a dynamical point of view, this can be formulated in terms of a second mode, faster than degradation, which dominates the transient excursion but which, being quickly exhausted, is not observable on standard turnover experimental curves.

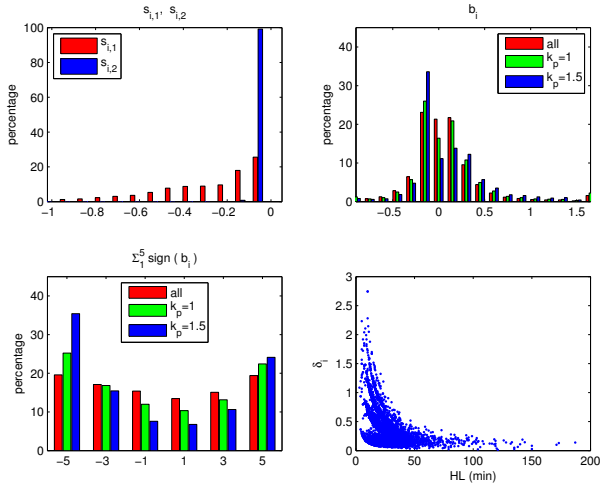

Fig. 4. On the top left panel the eigenvalues of the fitted system: $s_{i,2}$ is the decay mode corresponding to the known HL, $s_{i,1} < s_{i,2}$ ($s_{i,1}$, $s_{i,2}$ real). On the top right panel the values of fitted b_i (amplitude of the forcing term in the dynamical model), for all genes and for more selective thresholds on the maximal excursion of a gene: genes are considered only when $\max|log_2(m_i(t))| > k_p$, meaning that as k_p grows only the most perturbed genes are retained. For these the percentage of $b_i \approx 0$ decreases, implying that the forced response is more visible. Also the signs inferred for b_i (i.e., up/down regulatory effect of the 5 different u on the genes) are more concordant when the response is larger, see bottom left panel (where the sum of the ± 1 signs assigned for each gene to each u is shown). Notice that for at least 50% of the genes the sign assignement is unanimous (more than 70% for $k_p = 1.5$). On the bottom right panel the "true degradation rate" δ_i tends to be higher for genes with shorter HL.

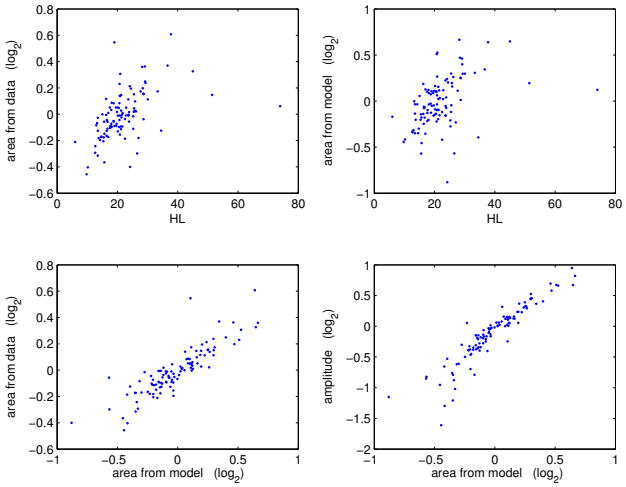

Fig. 5. Comparison between the area under the mRNA response measured on the data, area as obtained from the model (i.e., $p_i(t_{\text{end}})$), HL and maximal signed amplitude of the mRNA abundance, for the PC complexes of Fig. 3 (values are obtained averaging over all genes forming a complex and over the 5 time series). The high agreement between area (i.e., $\log_2(p_i(t_{\text{end}}))$) and the sign of the peak of mRNA during the transient (shown also in $\log_2$ scale) is a confirm that most transient excursions are not oscillatory.

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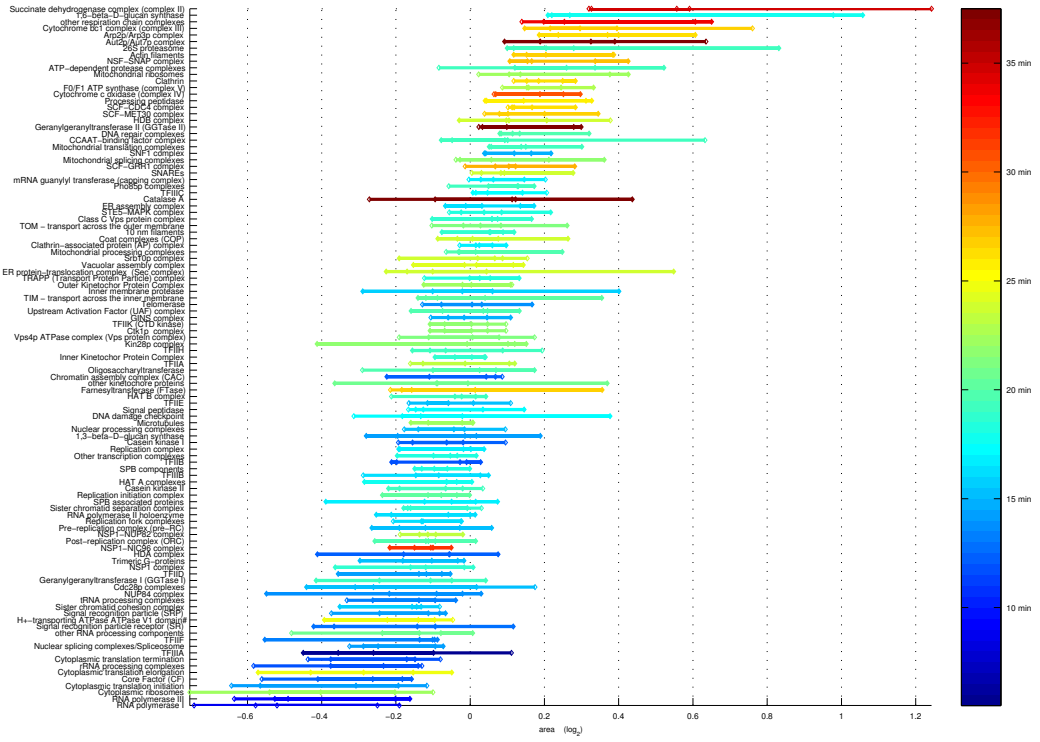

Fig. 3. List of significant PC and corresponding areas computed directly from the data for the 5 time series of Fig. 1. The solid markers represent the values in the 5 experiments. As can be seen, for most of the neatly up or down-regulated categories, the 5 values have identical signs. The color scale instead represents the value of HL associated to the protein complex: blue means short HL (minimum HL is 6 min) and red long HL ($\geqslant 40$ min).

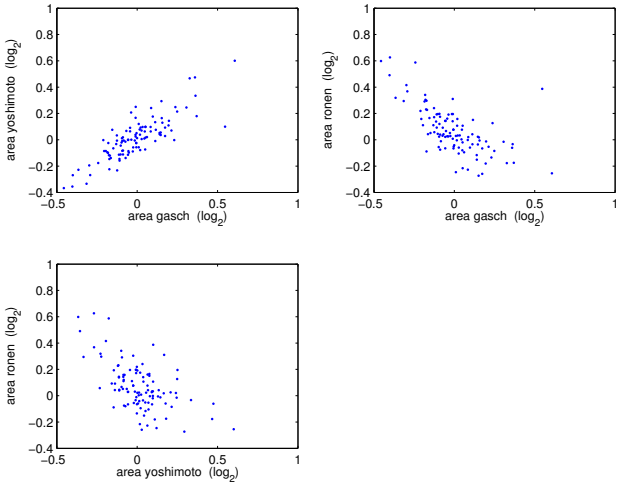

Fig. 6. Comparison of the average area for the time series of [3] (labeled "gasch"), [5] ('ronen") and [7] ("yoshimoto") for the PC complexes shown in Fig. 3. While "gasch" and "yoshimoto" are inhibitory stimuli (stresses), "ronen" are activatory pulses of nutrient. Hence the antidiagonal pattern in the areas shown in the middle and bottom plot.

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