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Sustained oscillations and time delays in gene expression of protein Hes1

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A number of genes change their expression pattern dynamically by displaying oscillations. In a few important cases these oscillations are sustained and can work as molecular clocks, as in the well-known cases of the circadian clock [1] and the cell cycle [2]. In other cases the oscillations in protein expression are connected with the response to external stimuli, as reported for protein p53 after induction by DNA damage [3] or as reported in association to specificity in gene expression [4]. Recently oscillations have been observed for the Hes1 system studied in the very interesting paper [5]. The Hes1 system is particularly interesting because it is connected with cell differentiation, and the temporal oscillations of the Hes1 system may thus be associated with the formation of spatial patterns in development.

Oscillations may be obtained by a closed loop of inhibitory couplings, provided that there are at least three different elements [5,6]. Alternatively, it was noted in the study of the p53 network [7] that a time delay in one of the components can give rise to oscillations also in a system composed of only two species (in this case, p53 and mdm2).

We suggest that time delay can be a general mechanism which produces oscillatory responses in a more economical way than three-species inhibitory networks do. A delay in a biological system can typically be related to transcription and translation times, and to transport between cellular compartments. An example is the Hes1 system recently examined in [5]. In this system the protein Hes1 represses the transcription of its own mRNA, and the system displays oscillations in both the concentration of the protein and of its mRNA. To explain this behavior, the authors of [5] suggest a third, hidden factor which would complete a three-species inhibitory network of the kind discussed in [6]. There is however no direct evidence for such a factor. Furthermore, since there is a non-negligible time for transport between the cell nucleus, where the protein controls mRNA transcription, and the cytoplasm, where mRNA is translated into the protein, we feel compelled to suggest a simpler scenario.

We want to test the hypothesis that Hes1 and its mRNA are sufficient ingredients to produce oscillations in the system. The equations for the concentrations [mRNA] and [Hes1] read

$$\frac{d[\mathrm{mRNA}]}{dt} = \frac{\alpha k^h}{k^h + [\mathrm{Hes1}(t-\tau)]^h} - \frac{[\mathrm{mRNA}(t)]}{\tau_{\mathrm{rna}}},$$
$$\frac{d[\mathrm{Hes1}]}{dt} = \beta[\mathrm{mRNA}(t)] - \frac{[\mathrm{Hes1}(t)]}{\tau_{\mathrm{hes1}}}. \quad (1)$$

The meaning of these equations is that mRNA is produced at rate α when Hes1 is bound to the DNA. The probability that Hes1 is bound to DNA is $k^h/(k^h+[\mathrm{Hes1}]^h)$, where k is a characteristic concentration for dissociation of Hes1 from the DNA, and h is the Hill coefficient that takes into account the cooperative character of the binding process. Moreover, Eq. 1 says that mRNA undergoes degradation with characteristic time τ_{rna}, that the production rate of Hes1 is proportional to the concentration of mRNA and that Hes1 is degraded on the time scale τ_{hes1}. Note that the terms associated with degradation in Eq. 1 not only describe the spontaneous degradation of the protein, but also the outflow caused by the protein going to interact with other parts of the cell.

The key point is that the production of mRNA is delayed by a time τ, which takes into account the lengthy molecular processes involved in the system (translation, transcription, etc.). If one inserts the delay in the production of Hes1 (the second of Eq. 1), instead that of mRNA, the results remain very similar to the ones reported here.

An important factor which determines the cooperativity in the production of mRNA is the fact that Hes1 is a dimer, and consequently we expect that the Hill coefficient h is of the order of 2. On the other hand, its precise value is not known. We have repeated our calculations for different values of h (i.e. $h=1.5$, 2, 4) and found that the system displays oscillations in all cases analyzed, although the detailed features of these oscillations (e.g. those displayed in Table 1) depend on the particular choice of h. This result agrees with the fact that the physical reason which causes oscillations is not the nonlinearity of the equations but the delay. In the following we analyze in detail the case $h=2$.

From [5], τ_{rna} and τ_{hes1} are of the order of 25 min. The value of the time delay is difficult to assess, since it is determined by a variety of molecular processes. One can guess that its order of magnitude is tens of minutes.

The solution of Eq. 1 is displayed in Fig. 1. For the chosen set of parameters, the system displays damped oscillations with period $\Delta\tau \approx 170$ min and damping time $\tau_{\mathrm{damp}} \sim 9500$ min. The dependence of $\Delta\tau$ and τ_{damp} on the delay τ is listed in Table 1. The oscillation period stays constant for a low value of the delay and increases as $\tau \gg \tau_{\mathrm{rna}}$. Also the damping time increases with τ, the oscillations becoming sustained for $\tau > 80$.

For any delay in the range $10 < \tau < 50$ min, the oscillation

Table 1
The damping time τ_{damp}, the oscillation period $\Delta\tau$ and the time difference between the peaks in hes1 and mRNA, as function of the delay τ

τ (min)	τ_{damp} (min)	$\Delta\tau$ (min)	$\Delta\tau_{\mathrm{peaks}}$ (min)
0	0	0	
10	450	170	18
20	500	170	18
30	870	170	18
40	1900	170	18
50	9500	170	18
80	∞	280	18
100	∞	360	18

Infinite damping time means that oscillations are sustained. For $\tau=0$ the system shows no oscillations.

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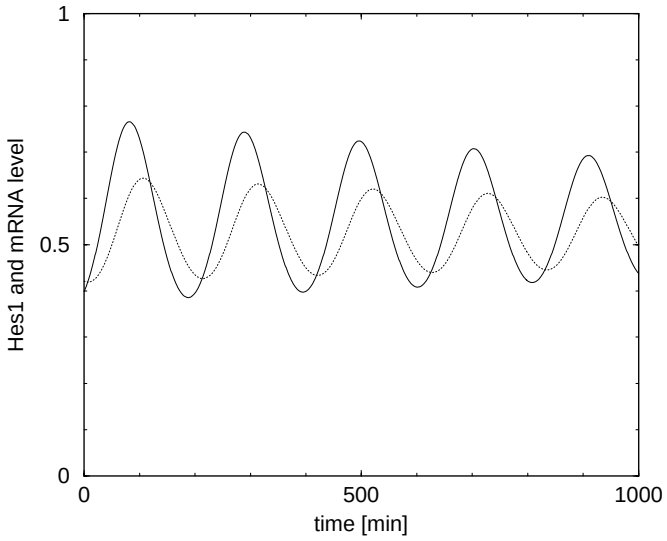

Fig. 1. The oscillatory behavior of the concentration [Hes1] of the protein Hes1 (dashed curve) and mRNA (solid curve), as calculated from Eq. 1. The following parameters are used: $\tau_{rna} = 24.1$ min, $\tau_{hes1} = 22.3$ min, $\alpha = 1$ $[R]_0$/min, $\beta = 0.1$ min^{-1}, $k = 0.1$ $[R]_0$, $h = 2$, $\tau = 50$ min, and the plot show concentrations in units of $[R]_0$.

period is consistent with that found experimentally, and also the time difference between the peaks in Hes1 and mRNA is 18 min, similar to the experimental findings. For $\tau < 10$ min, the system shows no oscillations. To check the robustness of the results, we have varied α, β and k over 5 orders of magnitude around the basal values listed in the caption to Fig. 1, and observed no qualitative difference with the oscillatory behavior described above. On the other hand, an increase of τ_{hes1} and τ_{rna} disrupts the oscillatory mechanism. This is because these two quantities set the time scale of the system, with which τ has to be compared. Increasing such time scales at constant τ is equivalent to decreasing τ for a given time scale, putting the system in the low-delay part of Table 1 where no oscillations are detected.

The time delay picture gives a natural description of the Hes1 network, without the need of additional unknown factors. This is the minimal model which, nevertheless, provides a very detailed agreement with the experimental findings. The delay summarizes a number of molecular processes, such as the time between transcription and final protein, the intracellular transport, or the time associated with the involvement of additional intermediates in the system. A striking overall result of our simulations is that the oscillatory period remains unchanged over a wide variety of values of the delay. Thus the observed time behavior mostly depends on the degradation times, whereas it is robust to variations in other parameters. This is functionally meaningful, since degradation times can be directly controlled by changing protease activities. In general, we speculate that, more than giving a description of the system, the time delay mechanism is a tool adopted by the cell to display oscillatory behaviors in an economic and robust way, making use of as few factors as possible.

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