(as occurred in the 1960s compared with the 1990s) promote deep convective mixing and vigorous mode-water formation: in a one-dimensional view[3], increased convection in the subtropical gyre should lead to stronger phytoplankton growth through the increase in nutrient supply. But Palter *et al.* argue that deep convective mixing in the area of Subtropical Mode Water formation in the 1960s severely diminished primary production in downstream regions because of the ensuing subsurface delivery of nutrient-poor waters.

The past 20 years have seen a great deal of research into how nutrients are delivered to the ocean surface. The variability of the subsurface nutrient reservoir has received much less attention: achieving a better understanding of that variability is one of the next challenges in marine biogeochemistry. ■

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SYSTEMS BIOLOGY

Deviations in mating

Avigdor Eldar and Michael Elowitz

Why do cells of the same type, grown in the same conditions, look and behave so differently? Studying fluctuations in a well-characterized genetic pathway in yeast hints at how such variation arises.

A glance in a microscope quickly convinces one that cells are strikingly diverse. Even when they share the same genome and are grown in the same environment, individual cells differ in size, shape and response to stimuli. Traditionally, such diversity has been a confounding factor in biology experiments, which seek to discover the precise response of a cell to a particular stimulus, but must instead contend with a multitude of answers. Improvements in quantitative single-cell methods and fluorescent imaging techniques now allow researchers to use the inherent diversity among cells to ask two questions: where does variation come from; and what can this variation tell us about the genetic circuits whose underlying components are fluctuating? On page 699 of this issue, Colman-Lerner and colleagues[1] confront these questions, reporting their quantitative single-cell analysis of a classic genetic network: the activation of genes in yeast cells in response to mating pheromone.

The yeast mating pathway has been characterized in great detail by beautiful genetic, biochemical and cell-biological experiments[2]. Yeast cells have two mating types: **a** and α. Stimulation of **a**-type yeast cells with α factor, the pheromone made by cells of opposite mating type, results in activation of a transcription factor (a gene-regulatory protein) called Ste12p. This protein in turn switches on a set of target genes by interacting with their regulatory sequences (promoters), which include one named P_{PRM1}. Stimulation eventually causes cells to adopt a 'shmoo' shape (a pear shape with one end elongated) as they seek a mating partner. Pathway output can be tracked by fusing the P_{PRM1} promoter to a 'reporter' gene encoding a fluorescent protein, so that activation of the promoter results in production of the fluorescent protein. All of this makes the mating pathway an ideal system to study at the single-cell level.

Colman-Lerner and colleagues observe that cells vary by about 35% in the amount of gene transcription that occurs in response to α factor. So where in the cell does this variation come from? One possibility is the inherent stochastic nature of the biochemical reactions necessary for expression of the reporter gene; this 'intrinsic noise' would be insignificant in a test tube but becomes significant at the small scale of the cell. Alternatively, the gene may be faithfully transmitting fluctuations ('extrinsic noise') in upstream components, such as the transcription factors that regulate it.

One way to discriminate between these two possibilities is to use genes that encode two fluorescent proteins — such as cyan fluorescent protein (CFP) and yellow fluorescent protein (YFP) — that can be distinguished but have the same regulatory sequences. If noise is transmitted from upstream regulatory components then, within each cell, the two colours should be expressed at an equal level, although this level may vary from cell to cell. However, if noise is generated by stochasticity in gene expression, the amounts of the two proteins will differ even within a single cell: they will become uncorrelated. Thus, in general, the level of correlation between the two reporter genes is determined by the relative significance of the two sources of noise (intrinsic and extrinsic). Such a noise-decomposition experiment directly tests how accurately a cell controls its own gene expression without feedback or higher-level circuitry. Similar assays, applied in yeast and the bacterium *Escherichia coli*, have detected both sources of noise and shown how their relative importance varies with gene, growth condition and expression level[3,4].

In yeast, stochasticity in reporter-gene expression, although significant, contributes much less variation than does that from upstream components[1,4]. Interestingly, previous experiments in yeast showed strong correlations between different promoters, suggesting that variation in one or more cellular components might affect diverse genes in a similar way[4]. Such fluctuations can be attributed to a hypothetical 'global' variable that is correlated with the overall growth rate of the cell and affects many processes, much like the health of a country's economy as a whole affects most stock prices[1,4,5]. Global fluctuations in gene expression might be related to fluctuations in the concentrations of polymerases or ribosomes — cellular components necessary for the expression of all genes.

Besides the magnitude of variation, the timescale of fluctuations is also important. Colman-Lerner *et al.*[1] report that the responsiveness of a cell to α factor is approximately constant over a long timescale of many hours. This is similar to recent observations in *E. coli* showing that the dominant fluctuations are slow, with typical timescales on the order of the cell-cycle time[5].

The authors attempt to take noise decomposition a step further by introducing a phenomenological model that subdivides transmitted (upstream) noise into two hypothetical categories: global and mating-pathway-specific (Fig. 1a, overleaf). To do this, they built a yeast strain containing the gene encoding YFP under the control of the mating-specific P_{PRM1} promoter and the gene encoding CFP under the control of the pheromone-independent actin promoter, P_{ACT1} (Fig. 1a, top). In such a strain, a high degree of correlation between the two promoters would suggest a common 'global' source of noise; a weak correlation would suggest independent noise sources (Fig. 1a, bottom). Hence, the correlated part is attributed to global noise, whereas the uncorrelated part is attributed to pathway noise.

So where does noise in the mating response come from? The answer is that it depends on the conditions. Experiments performed with different amounts of pheromone show different results (Fig. 1b). At high pheromone concentration, variations in P_{PRM1} expression correspond closely to variations in P_{ACT1} expression. One explanation for this might be that a component of the signalling system has become saturated and hence does not transmit variation in components upstream of it (in fact, Fig. 2b of the paper shows that the mating

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50 & 100 YEARS AGO

50 YEARS AGO

"Man and his machines" — After expressing the fear that technical colleges are not educational institutions but teaching shops, [Mr Harry Rée] emphasized that "in building a world where machines do the work which used to be done by men, it is not good enough to build men who can only work like machines"...

He concluded by envisaging the great contribution educational institutions could make by a counter attack on the creeping disease of passive pleasures which is eating away the soul of modern man. "If we could make the effort...we should look upon automatic factories and computing machines as our benefactors enabling us and our children to taste to the full the real joys of life."

From *Nature* 1 October 1955.

100 YEARS AGO

"The omission of titles of addresses on scientific subjects" — What this busy world wants is help to get at what we are interested in with the least possible waste of time.

This hot haste may seem unbecoming to men of science, or perhaps it may appear that we Americans are in too big a hurry — that we are too much impressed with the motto "time is dollars." But there are many other nimble things we are trying to keep up with, and one of those is the progress of science in Europe, along the lines in which we are especially interested.

If a member of so young and giddy a nation might venture to make a suggestion to older and wiser people, it would be in favour of requesting or requiring the presidents of the various scientific organisations and sections of the British Association to provide headings for their addresses so that those of us who have not the time to read all of these good things may be able at a glance to pick out what we want especially to see.

From *Nature* 28 September 1905.

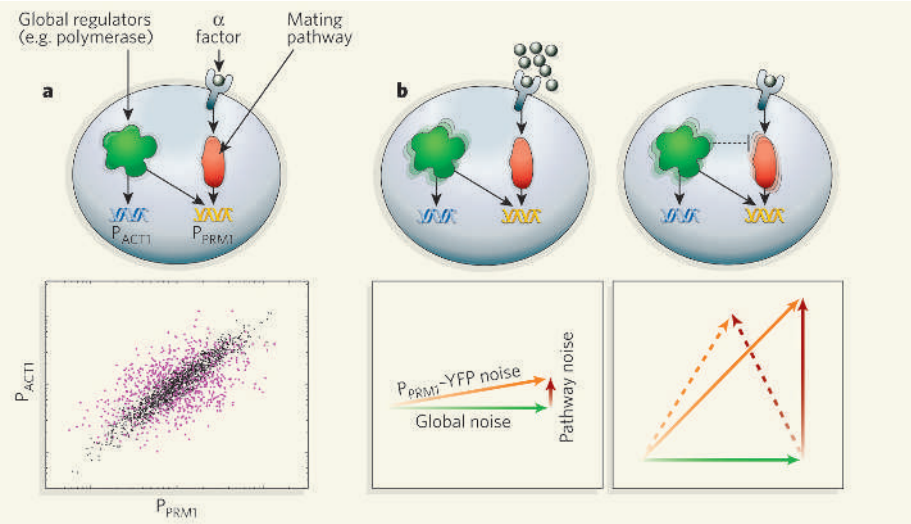

Figure 1 | Noise decomposition in the model of cell behaviour devised by Colman-Lerner and colleagues[1]. **a**, Upper panel, global regulators (green) affect expression of all genes, including that encoding cyan fluorescent protein regulated by the P_{ACT1} promoter and the gene encoding yellow fluorescent protein (YFP) under the control of P_{PRM1}. The mating pathway (red) affects only P_{PRM1}. Lower panel, expected results in two extreme cases: total P_{PRM1} noise may be dominated by global factors (black points) or by pathway noise (magenta points). **b**, Noise depends on pheromone levels. At high concentrations, noise is dominated by global fluctuations, resulting in strong correlation between the two reporter genes (left). In the vector diagram, coloured arrows represent noise amplitudes and their degrees of correlation with other noise sources. At low pheromone concentration (right), there is reduced correlation between the two reporter genes. Within the model, this is interpreted as an increase in pathway-specific noise. If the two noise sources were independent, the magnitude of P_{PRM1} variation would increase (orthogonal solid arrows, bottom panel). However, the authors observe that the magnitude of the P_{PRM1} variation is independent of pheromone concentration, implying a negative interaction between the two noise sources (acute angle between green and dashed red arrows).

pathway is saturated under these conditions[1]). In this case, fluctuations in P_{PRM1} are dominated by the global factors referred to earlier.

But what happens at low pheromone levels? Under these conditions, the authors observed reduced correlation between the two promoters (Fig. 1b, right). If pathway-specific noise were independent of global noise, one would expect the variance in P_{PRM1} activity to be the sum of global and pathway-specific variances (orthogonal green and red arrows in Fig. 1b). This would result in an increased total noise in the P_{PRM1} promoter compared with its value at high pheromone concentration. Interestingly, such an increase is not observed[1]. The missing noise indicates the existence of a negative interaction between global factors and the mating pathway (green and non-orthogonal dashed red arrow in Fig. 1b). The authors interpret this negative interaction as a buffering of pathway noise by the effects of global noise on genes in the mating pathway.

The existence of such an interaction is not surprising: being global, such factors should affect other genes along with components of the mating pathway. However, many regulatory steps may connect the global factor to pathway components — the sign and magnitude of this arrow is not clear. It will be interesting to find out whether the inferred buffering interaction has adaptive significance. This could be explored by examining the response of other mating-pathway targets and the effect of variation on the physiological behaviour of mating. How widespread the buffering is could be examined by similarly analysing other pathways.

In general, correct interpretation of noise experiments can be subtle[6]. For example, the buffering interpretation described above depends on the implicit assumption of the model that global noise affects the P_{PRM1} promoter equally at both pheromone levels (that is, the green arrows in Fig. 1b are equal). In the future, it may be possible to develop higher-resolution analysis of noise correlations, allowing phenomenological models to be replaced by molecular ones. In physics and engineering, analysis of fluctuations often provides unique insights into the dynamics of a system. Normally, such an analysis is limited by the amount of variation present in the system to begin with. Luckily, with living cells, there is no lack of noise to work with. ■

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