



Figure 1 Structure of the t complex and its proposed action on sperm function. **(a)** Structure of the t complex on mouse chromosome 17 showing the four inversions and the approximate locations of the distorters and responder. The positions of the responder gene *Smok1* and the new distorter *Tagap1* are also shown. Below is the haplotype t^6 , which has wild-type chromatin in place of *In(17)1* and *Tcd1* and was used by Bauer *et al.* in their tests³. The percentage transmission of a complete t haplotype and t^6 are also shown. WT, wild-type. **(b)** Action of *Tagap1*, *Tcd2* and *Tcd3* on a wild-type and a t sperm cell. The distorters act on both wild-type and t sperm but *Smok1^{Tcr}* is resistant to their action.

But previous results showed that a deletion, T^{22H} , thought to remove *Tcd1* mimicked the action of *Tcd1*, indicating that *Tcd1* was an amorph or hypomorph⁵. Herrmann and colleagues suggest that this discrepancy results from the presence of more than one distorter in the *Tcd1* region. Further studies of deletions suggested that *Tcd1* consisted of at least two genes, *Tcd1a* and *Tcd1b*^{6,7}. It is proposed that *Tagap1* represents *Tcd1a* and that *Tcd1b* is a hypomorph. Further work is needed to resolve this puzzle. In addition, we do not yet

know the roles of *Tcd2* and *Tcd3*. Various candidate genes have been proposed to underlie them². Are they part of the signaling cascade, or do they have other functions?

Another question concerns male sterility. The current view is that the sterility of males doubly heterozygous or homozygous with respect to regions of the t complex is due to homozygosity with respect to the distorter genes themselves⁸. Herrmann and colleagues have not studied effects on fertility, and so this question remains open as far as *Tagap1* is

concerned. Thus, the work of Herrmann and colleagues is a step forward, but the t complex has not yielded all its secrets yet.

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Prime movers of noisy gene expression

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Molecular noise, or random fluctuations in the levels of cellular components, arises spontaneously when there are small numbers of molecules and is transmitted to dependent processes. A new study shows how noise propagates through gene expression in yeast and shows that chromosomal position has a more central role than previously thought.

Genetically identical cells growing in the same environment still vary greatly with respect to their internal protein concentrations. Several studies^{1–6} have shown how these fluctuations arise intracellularly and then propagate through reaction networks. The question is where in the cells they originate. What ‘prime movers’ first generate the noise and set all downstream components into motion?

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On page 937 of this issue, Alexander van Oudenaarden and colleagues⁷ show that the position of the genes along the chromosome can be more important than the number of transcripts or proteins in this process.

Sources of noise

Unlike Aristotle’s Prime Mover hiding behind the stars, the original sources of protein noise might not be far away. Tens of thousands of macromolecules are present at a few copies per cell, numbers so low that large relative fluctuations arise simply because individual chemical events rely on collisions between randomly diffusing molecules. Protein noise

could come directly from having few protein copies, but because low concentrations are hard to measure, this has not yet been explicitly demonstrated. It could also be transmitted from having few transcripts^{1,8–10}, random activation-inactivation of the genes^{3,4,11} or fluctuations in any other factor that indirectly affects protein synthesis or degradation^{2,12–14}. The hunt for prime movers is therefore complicated by the abundance rather than absence of plausible candidates.

Chromosomal position

One way to narrow the options is to identify upstream components present in low

numbers and test whether increasing their levels reduces relative fluctuations^{1,13}. For example, if protein noise came entirely from having few transcripts, it should decrease with the rate of transcription (increasing mRNA numbers) but not with the rate of translation (increasing only protein numbers)¹. Becskei *et al.*⁷ used a version of this strategy to investigate SWI promoters involved in the yeast cell cycle. They noted that some mRNAs are present in as few as 0.005 transcripts per average cell, moved genes on the chromosome and measured how relative fluctuations depend on expression rates. In an experiment in which changing the gene location doubled the expression rate, they observed close to the expected noise reduction by a factor of $\sqrt{2}$. But when they inserted five gene copies in tandem or introduced a gene pair at homologous chromosomal sites of a diploid cells, the effects were negligible. These results suggest that protein noise is not inherently determined by the transcript level and instead that noise and transcript level merely correlate in certain experiments. Therefore, although the mRNAs may be disguised as the puppeteers regulating protein noise, Becskei *et al.*⁷ show that they are only dancing in the hands of a second puppeteer, working through the chromosomal positioning of the genes.

Intrinsic versus extrinsic noise

The strategy above indirectly tests whether individual gene copies behave as independent units or depend on upstream events. Another method to distinguish between these alternatives is based on the coexpression of dual reporters^{2,4,12}. Genes filter extrinsic fluctuations in the state of the cell through their own intrinsically random expression mechanisms, like erratic thermometers approximate changes in temperature. How much of the fluctuations are intrinsic to the thermometer and how much are extrinsic to the environment? One way to find out is to place another thermometer next to the first. Although this does not allow measurement of the actual temperature, the variance can be inferred from the covariance between



cartoon by Sean Taverna

the read-outs: strong and weak correlations come from extrinsic and intrinsic fluctuations, respectively. This method is useful but has two drawbacks in intracellular applications: it does not work in nonlinear systems where the copies contribute to each other's environments, and it requires the two genes to be identically expressed. By showing that the same gene copies at different chromosomal positions have different noise properties, the results from Becskei *et al.*⁷ caution against using dual reporters without first carefully testing that they indeed are identical. Such tests were done in the first dual reporter studies^{2,4} and must be carefully repeated in all future work.

Outlook

The results of Becskei *et al.* raise several questions. First, if the prime movers are not low-copy mRNAs, then what are they? Few candidates would target a whole stretch of chromatin rather than a single gene and also strike in a correlated fashion at the same address (but not at a different address) on other chromosomes. Second, how specific are these phenomena to the SWI promoters studied? Are they restricted to cell-cycle genes, or are they a general feature of eukaryotic gene

expression? Third, is the absence of substantial low-number mRNA fluctuations due to some unknown control circuit, or are individual transcription and mRNA decay events less random than previously thought?

This last question touches on one of the most underaddressed issues in quantitative molecular biology, relating to the stochastic properties of the prime movers. Births and deaths of macromolecules do not necessarily occur through memory-lacking 'exponential' transitions but often involve many small steps. This could reduce fluctuations without any control loops and may explain why low transcript levels do not necessarily invoke large relative fluctuations. The problem is that such effects are very difficult to demonstrate experimentally. Studies using green fluorescent protein reporter constructs have been used to estimate shapes of protein distributions, but to settle the issues above, future studies may have to 'count' the integer numbers of both mRNAs and proteins.

The most central questions are therefore still unanswered: what are the prime movers, and what type of stochastic events define them? The results of Becskei *et al.*⁷ point in some unexpected directions, and more surprises are probably in store.

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