

## On the use of metaphor to understand, explain, or rationalize redundant genes in yeast

Stephen Cooper

Department of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, MI, USA

**Correspondence:** Stephen Cooper, Department of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, MI 48109-0620, USA. Tel.: +734 764 4215; fax: +734 764 3562; e-mail: cooper@umich.edu

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### Introduction

When ideas are encapsulated in proverbs or metaphors, sometimes there are contradictions. For example, consider the adages, 'too many cooks spoil the broth' and 'many hands make light work.' Each proverb has an element of truth, but one must know that it is not an absolute truth.

Sometimes metaphors, like proverbs, are used to explain or rationalize experimental results. In immunology the 'lock and key' metaphor tried to explain how antibodies and antigens might combine due to complementary surfaces. The field of genetics is sometimes encapsulated by the apple image in the proverb 'the apple doesn't fall far from the tree.' The question then arises, does this metaphor really fit, or is there another metaphor that can apply.

I write to comment on an explanation of a genetic analysis from the Boeke laboratory (Pan *et al.*, 2006) on the identification of genes that appear to be redundant in *Saccharomyces cerevisiae*. It must be emphasized that I am not presenting a critique of the enormous amount of work and effort that went into the identification of genes that appear to be able to cover similar functions. I believe that the work of the Boeke laboratory is superb and deserving of note. But there are three points that must be raised, one

### Abstract

The proposal that yeast, and cells in general, contains redundant genes that enable cells to survive mutational change has been supported by experiments and a strong metaphor. The redundant gene proposal is analyzed, and it is noted that there are many problems with the redundant gene model. An alternative metaphor is suggested to explain the genetic composition of a yeast culture.

regarding the general rationale of the result, one regarding the deeper implications of the result with regard to yeast cell studies, and a final one regarding the evolutionary implications of this result.

Simply described, the Boeke group looked at cells with one gene missing that were still able to grow, and then looked in these cells for other genes that when mutated would lead to a lethal effect. Genes were identified that were only lethal in the absence of another gene. This work led to the identification of numerous gene groups that were proposed to give the cell a robust response to various stresses, in particular the mutation or destruction of a particular gene. If two independent genes can serve the same or similar functions, then the cell has a response to the introduction of lethal mutations to a specific gene.

In an article about the result published in *Microbe*, the magazine of the American Society for Microbiology (Holzman, 2006), there is a description of the result and the presentation of a metaphor to rationalize or explain the result. After a short description of the basic findings, a metaphor is introduced to support the idea of redundancy in genes leading to survival even after some genes are eliminated by mutation. Thus, after noting that 'Thousands of pairs of genes in the yeast *Saccharomyces cerevisiae*

mutually back up one another, one compensating when the other member of a pair develops a defect . . .', Boeke proceeds to give the following explanatory analogy or metaphor:

' . . . a bus and the subway are transporting school kids to the museum. A power outage (loss of one pathway) takes the subway out of commission, but the children on the subway can still crowd into the bus. But if the bus also gets sidelined, due to a flat tire, bad brakes, an electrical problem, or a broken axle (loss of one gene in one of the many pathways that keep the bus going), there will be no field trip.'

As Boeke's analogy implies, an individual gene can have backup relationships not only with one gene, but with many. Thus, the subway can back up the bus's brakes, axle, electrical system, and tires.

To give a concrete example, Boeke discusses DNA replication, a complex process involving several pathways. Boeke notes, 'If you mess up DNA replication by mutating some gene that contributes to its fidelity, it can lead to lots of errors and breaks in the DNA.' The cell therefore contains 'backup' pathways that prevent cell death. For example, a DNA replication checkpoint would arrest the cell cycle to enable DNA repair to occur before proceeding to division.

One surprising result emanating from the experiments is that the Golgi apparatus appeared to be involved in maintaining DNA integrity. This finding is surprising, because this organelle serves mainly to direct molecules to their proper places within a cell.

I will analyze this rationalization of the redundancy of genetic information from three points of view. First, I will present a different metaphor to consider when thinking about how a cell may respond to mutational loss of gene function. Then I will discuss the deeper implications of the results that lead to problems not generally considered by the field regarding redundant genes, specifically with regard to the problem of what is a normal, wild-type cell. Finally, I will briefly consider the evolutionary implications of this result, or rather the proposal of redundancy among genetic functions.

### An alternative metaphor

Consider a factory that manufactures paper clips, those little curved pieces of metal that hold two pieces of paper together and which are inexpensive and available in large numbers for a moderate cost. As the factory makes these paper clips, consider that there are occasional errors in production, and a twisted or incorrectly bent paper clip is produced. How would this be handled? One way is to have a machine check the paper clips produced by the factory, and when an incorrect paper clip is found, the machine would fix the paper clip and put the repaired paper clip back into the packaging line.

But an alternative approach is to just forget about repairing the paper clips and to discard the broken ones. After all, they are so inexpensive to produce, why employ an expensive machine to repair a rare 'mutant' paper clip when just discarding it would be satisfactory.

It is probably safe to say that the manager of the paper clip factory would just accept errors, and move forward with the correct paper clips and ignore the bad ones.

Yeast divides every 90 min, and millions of yeast cells can be produced quite quickly. One can therefore ask, 'Why would a cell culture or large group of cells worry about a single individual cell that has an error, and carry forward machinery that would allow such an injured cell to live and grow?' After all, as there are so many yeast cells, what does the yeast population need with one more cell. A rational view of the calculus leading to the most efficient and best yeast population would ignore the death (by mutation) of one individual cell and just let the remainder of the population move forward. To paraphrase a famous American Admiral, 'Damn the torpedoed cells, full speed ahead.'

It may be that the need to save each injured or mutant cell reverberates in the normal human response to problems with other humans. We apply all of our energies to keep many ill human beings alive, and do not discard them even though there are many other human beings around. But we should not apply this normal humanitarian feeling to the problem of yeast growth, where it may be better, in the long run, to eliminate various problematic cells in order to ensure the genetic health of the entire population.

Thus, the rationale to explain the appearance of redundant functions does not seem to be explanatory at all. I do not know the ultimate meaning of the Boeke group result, but it is not clear that a cell would employ methods to protect damage to every gene or many genes. Nor is it obvious that a cell would maintain a complex 'backup' system of redundant genes in order to allow cells that have some mutational stress to survive and grow.

### The deeper problem: what is a common strain of yeast?

More crucial is the problem that arises if cells have mutations that are covered over by redundant genes. Let us say that this was the case. Then when a particular clone of yeast is isolated, one never knows whether that particular cell is representative of the natural and original yeast population. That is, in any yeast culture there would be many cells that would grow and would be different from other cells because they harbor particular mutations. But these mutations are unseen because they are covered over by the redundant genes in the cell.

How could the yeast cells handle this to make sure that the culture is a uniform population of yeast cells. One way is

the repair, in a nonrandom way, of the mutations. Consider what this would require. Upon growth of the mutated cell (because it can grow as the function is covered by the other, redundant genes), a number of mutated cells would be produced. In order to repair the mutation, all of the progeny of the original mutant would have to repair that initial mutation. This would mean that a hidden mutation, not affecting the cell growth, would be specifically repaired by some system to return the progeny of the original cell to a normal cell genotype, with 'normal' meaning the genotype present before the mutation.

Alternatively, and what I suggest is most likely, the culture would grow with the mutant cells, and this would mean that any time one cultured a yeast from a single cell there would be a chance that that cell would have a hidden mutation that would make it different from all of the other yeast cells that other laboratories would be working with. The concept of a common strain of yeast that all labs work with would be lost.

Jef Boeke (personal communication) has pointed out that other laboratories, working with yeast strains that have been separated for over 10 years (and thus are separated by thousands upon thousands of generations of growth), obtained results similar to that from his laboratory. Boeke points out that such differences as expected by the redundancy in cells does not lead to the maintenance of differences in yeast strains. But this result has an alternative implication. If there are no apparent uses of the redundancies in cells – that is, cells do not appear to utilize the redundant functions to enable mutant cells to grow despite some gene being damaged – then one can ask, why should a cell have redundant genes? If one cannot find the use of the redundancies in normal populations, one can then ask, what is the use of such redundancies. The finding that cells do not diverge in genotype can be interpreted in two ways. As Boeke suggests, there is not much of a problem stemming from redundant genes, and thus in practice the problem of what is a wild-type yeast strain does not arise. The alternative interpretation is that if one does not find such a use of redundancies in normal cells, then one must question the utility and meaning of the finding of redundancies.

It has been suggested (anonymous reviewer) that mutations or replication errors are occurring all the time in growing cells, and that cells in a culture are therefore genetically heterogeneous. While I agree that replication errors are occurring all the time, I suggest that the parental yeast cell from which a culture is descended produces a culture with cells that are like the parental cell. That is because the evolved yeast strain is presumed to be the product of many generations of selection. Mutants are therefore more than likely slower growing than the parental cell. With growth, these mutants are selected away and are lost. (Of course, the rare cell that grows faster than the

parent will eventually take over, and this is the source of evolutionary development.)

## Evolutionary implications

For a cell to carry forward many redundant processes, it is presumed that these processes enable the cell to be favored in evolution. That is, it must be assumed that the benefit to the cell of this redundancy is more valuable than the costs to the cell for maintaining the redundancies. If we were ever to be able to calculate the costs and benefits of some system, it is assumed that a biologically favored system would be one where the benefits outweigh the costs. It is hard to imagine, from one anthropomorphic view, whether this benefit to the yeast cells is worth the costs.

For evolutionary considerations as well, one should therefore be skeptical of the ultimate meaning of the Boeke laboratory's results. Again, it is not argued that the results of the Boeke laboratory are incorrect or not important. It is argued, however, that the concept of redundancies in the genome to allow cells with damaged genes to survive needs further skepticism.

On a more general level, if we consider that a cell has two genes that can cover the same function, it is likely that one is better than the other with respect to supporting growth. This would lead, over many generations, to the selection of the superior function and the loss of the other redundant function.

It is important to recognize that this discussion does not consider redundancies due to genetic duplications, where the redundancy is related to the presence of two copies of the same gene. The presence of gene duplications, either next to each other or in other parts of the genome, can lead to a trivial result where there is a requirement for two mutations to produce a particular effect. The discussion here is limited to redundancies where the protecting, compensating, or redundant functional gene is a completely different gene than the protected gene.

## Reinterpreting the results

I am not able to do better than the Boeke laboratory at interpreting their results. My presentation here is merely to raise a red flag and to hint that one should take the Boeke result and consider alternatives. In fact, considering some of the precise results obtained, one should be cautious and perhaps even a little skeptical of the general idea of a wide range of redundant functions. For example, the surprising finding that the Golgi apparatus is involved in maintaining DNA integrity could be taken, not as a result to be accepted, but as a result to suggest that perhaps there are deeper and different interpretations of how cells respond to genetic alterations.

To give a simple view of how one could be misled, consider the classic bacterial phenomenon of thymineless death. When bacteria are starved of thymine they die. However, if one inhibits mass synthesis, cell killing is inhibited. It is now known that the unbalanced growth of the cells leads to their cell death. If one mitigates this unbalanced growth by slowing or stopping cell mass synthesis, then cells that do not have thymine are spared from death. One could imagine that a bacterial cell with a slight thymidine impairment that could lead to death would be rescued by a slight impairment in overall growth rate. In the reverbalization of the thymineless death phenomenon, we could say that limiting thymine is protected by mutations in genes that slow down cell growth. Any function that leads to slower growth would reduce thymineless death. I do not present this scenario to suggest that this occurs in yeast, but merely to point out how one may think about the results of Boeke without invoking the idea of redundant functions.

Employing this type of reasoning for the yeast study, one could imagine that slight impairments in unrelated cell functions could lead to the apparent rescue of cells from death.

## Summary

The ideas presented above suggest that despite the clear and enormous work of the Boeke laboratory, one should be reserved about accepting all of the redundancy proposed to exist in yeast. Until some of the questions raised here are dealt with, it appears that other explanations may be in order.

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