



# The secret life of a cellular business

What does a cell have in common with a thriving business? More than you might think says Dr Stefan Klumpp – and it's all down to the economic principles of physiological decision-making

In high school textbooks, cells are often compared to factories that contain a plethora of different machines, power plants and delivery systems. Growing and proliferating cells have to make all these machines for their daughter cells, so taking the metaphor of the cell as a factory a step further, one can compare them to an expanding company that has to make investment decisions. A key investment decision in rapidly growing cells (bacteria and yeast, but possibly also proliferating mammalian cells) is how to use the cell's ribosomes. Cell growth and proliferation is closely linked to protein synthesis, because growing cells have to make large amounts of protein. For example, in rapidly growing bacteria, half of the cell's mass is protein and protein synthesis accounts for up to two-thirds of the cell's energy consumption. In exponential growth, all cellular protein needs to be doubled within one doubling time, so the molecular machines that power protein synthesis, the ribosomes, have to work at a very high rate.

**The most striking** evidence for the close link between cell growth and protein synthesis is the perfectly linear relationship between

the cellular ribosome concentration and the growth rate, which was discovered based on the systematic characterisation of bacterial growth and its effect on the cells' chemical composition in the late 50s. For example, *E. coli* cells have been grown in different growth media that contain different nutrients and for each medium the growth rate and the ribosome concentration was measured. If the ribosome concentration is plotted against the growth rate, a very simple linear correlation is found (Figure 1), despite the fact that the regulation of ribosome synthesis is very complex. The linear relation can be interpreted as reflecting the autocatalytic activity of ribosomes making ribosomal proteins. Thus, at rapid growth, cells devote more ribosomes to making ribosomal protein than at slow growth. This idea has been developed into a quantitative theoretical description of cellular resource allocation by Matt Scott et al. in an article published in *Science* in 2010, realising that the cell has to balance conflicting requirements<sup>1</sup>. It would be advantageous for cell growth if the cell could devote a fraction of ribosomes as large as possible to making ribosomal proteins, but devoting many ribosomes to making enzymes that import and process nutrients is also advantageous for cell growth. The two fractions cannot be maximised at the same time, but rather the cell has to find a balance between these requirements. Using another concept from economic theory, this balance has recently been interpreted as a case of Pareto optimality, where any improvement of one objective results in a setback for another objective<sup>2</sup>.

**In industrial production**, companies can react to a slow-down in demand either with lay-offs or by reducing the workload (working hours) per worker. Cells facing a slow-down of nutrient availability have the corresponding choices with their ribosomes. They can reduce the ribosome concentration or make the ribosomes work at a lower rate. Likewise, they can react to an improvement of the growth conditions by increasing the ribosome concentration or by increasing the rate at which ribosomes work. It turns out that *E. coli* uses a combination of the two strategies, increasing or decreasing ribosome concentration and translation speed together. Which strategy is used was the subject of a long-standing controversy, as the linear relationship between growth rate and ribosome concentration has traditionally been interpreted in terms of a constant translation speed, inconsistent with direct observations. However, recent analysis has shown that the two are indeed consistent if the interpretation of the linear relation is slightly modified<sup>3</sup>.

From the viewpoint of economic allocation of ribosomes, the modulation of the translation speed indicates that high translation speed also comes at a cost for the cell. Otherwise the big investment that is the cellular ribosome pool would be used quite inefficiently, as the ribosomes could work at higher speed without additional cost. Indeed, a cost can be attributed to the translation speed, because high rates of translation require additional proteins to be synthesised. The most important of these is elongation factor Tu (EF-Tu), which delivers tRNAs carrying the amino acids needed for protein chain elongation to the ribosome. EF-Tu is the most abundant protein in rapidly growing *E. coli* cells,

where it can account for up to 10% of the total protein mass. This means that the cell again has to balance different requirements, making many ribosomes and making them fast, that cannot both be optimally satisfied at the same time. A recent theoretical analysis<sup>3</sup> of that balance shows that a simple strategy for almost optimal use of the cellular resources is to couple the speed-related proteins such as EF-Tu and tRNA synthetases closely to the ribosomes and to increase their synthesis whenever the ribosome synthesis is increased. Indeed, in bacteria the genes encoding these proteins as well as the tRNAs are often located in operons together with ribosomal components and thus regulated in a similar fashion.

**Why is it costly** for the cell to increase the speed of translation? Rapid translation requires that EF-Tu delivers tRNAs carrying the amino acids to the ribosome at a high rate. This rate, however, is limited by a physical constraint. The cytoplasm is a crowded place, filled with proteins and other macromolecules, and therefore diffusion of the big complexes of EF-Tu and tRNA is quite slow. The only way to make them arrive faster is to have lots of them, so one of them may get to the ribosome in time.

Understanding the economic strategies of how to allocate ribosomes to making different types of proteins is not only interesting as a basic research question. For example, in biotechnology, bacteria are often used for the recombinant expression of heterologous proteins. From the point of view of the bacteria, this task is not much more than a gigantic waste of ribosomal resources and thus leads to a slow-down of growth that becomes more and more pronounced with increasing levels of expression of the 'unnecessary' protein. Thus, taking into account the internal economic principles of the cell may help increase the yield of expression. Moreover, aspects of the proteomic economics may be useful for understanding the action of antibiotics and improving treatment strategies. Bacterial ribosomes are the target of a large number of antibiotics. Typically the cells react to such drugs by making more ribosomes to partly compensate the reduced ribosome function (provided that the dose is sufficiently low to not kill the cells immediately). Other types of antibiotics lead to different responses, for example drugs targeting DNA replication. Combining antibiotics that induce conflicting responses has been proposed as a strategy to enhance the cooperative effect of the two drugs<sup>4</sup>. For example, ribosome synthesis is down-regulated when DNA replication is impaired. This down-regulation prevents the compensation for reduced ribosome function if a ribosome drug is administered in addition to a drug targeting DNA replication. Thus, one drug (blocking DNA replication) effectively makes the cells more susceptible to the second drug (targeting ribosomes). In effect, low doses of the two drugs may have a stronger effect than a high dose of either antibiotic alone.

Economic constraints such as those discussed here for ribosome synthesis and function apply to many physiological situations, so similar approaches can be expected to be fruitful for other problems as well. Indeed, a recent study has addressed the coordination of the carbon and nitrogen metabolism based on considering the growth-rate dependent expression of the corresponding enzymes<sup>5</sup>. Approaches of this type that combine the quantitation of cell growth with economic considerations of the proteome can tame the complexity of the underlying molecular control by directly addressing physiological responses rather than the multiplicity of molecular interactions. Moreover, similar considerations can be applied to all kinds of cells, as long as they are rapidly growing and proliferating, so similar studies should provide insight into the economic principles used by proliferating cells in higher organisms, in particular during embryonic development or in tumours. **LN**

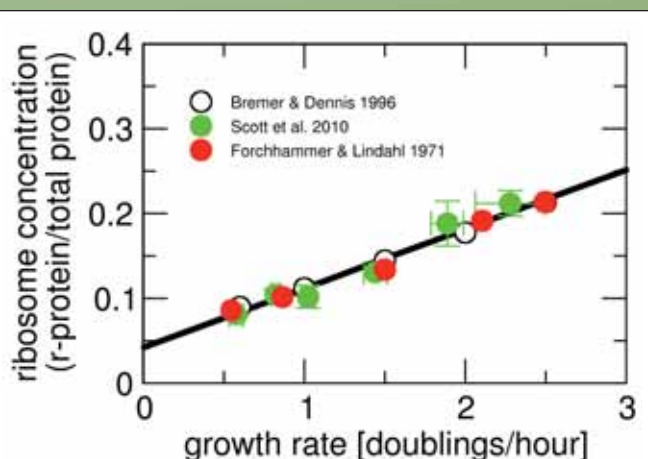
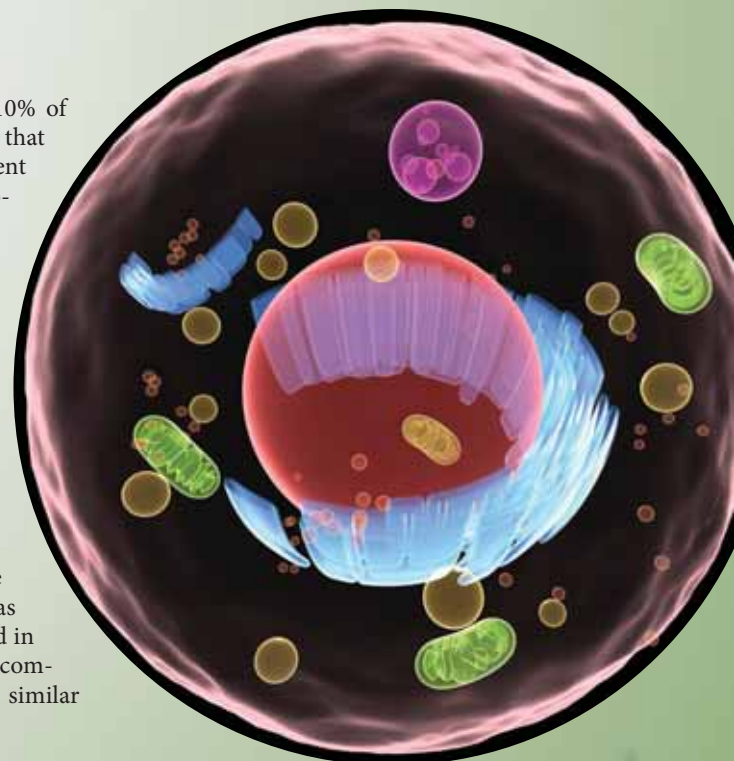


Figure 1: Relation between ribosome concentration and growth rate for *E. coli* grown in media with different nutrients.

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