Order out of Chaos

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Living cells are essentially just sacks filled with molecules, most of which move around freely, pulled around by random thermal motions. And yet different cells fulfill extremely precise functions in living organisms. How does the randomness of inanimate matter become a highly organized living tissue?

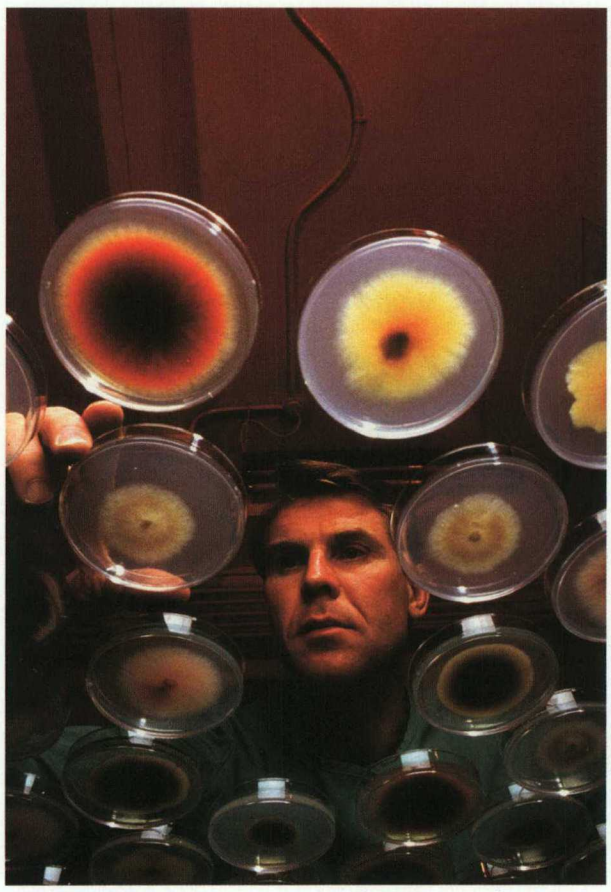
Is it possible for a computer to be capable of assembling itself? How about if we consider a living cell from this perspective? Systems biology is a new interdisciplinary field of study that straddles the boundaries between biology, physics, and chemistry, using tools drawn from statistics and IT. It looks at living cells as complex signaling systems, not dissimilar to electronics systems; they send and process signals, and there are even logic gates. At the same time, however, cells are greatly unlike inanimate machines in many ways: they self-organize and use random perturbations to their advantage.

I am one of the few scientists in Poland working in this recently developed field. In late 2010, my colleague Dr. Marcin Tabaka and I published a paper in the prestigious journal *Proceedings of the National Academy of Sciences* (PNAS). In 2010, PNAS published just 9 papers co-authored by scientists from Polish research institutions; our paper was the only one prepared exclusively at a Polish institute.

On one hand, the latest experimental techniques now make it possible to study the motion of individual molecules within a cell. On the other hand, researchers are nowadays able to conduct large-scale automated experiments using bioinformatics to reveal statistical dependences between the simultaneous actions of thousands of genes. Systems biology makes it possible to describe the function of living cells in terms of networks sending signals, which means that research into the properties of the basic building blocks in this network - the simplest gene regulation systems - is becoming increasingly important.

The rule of chance

We developed and published a theory, based on statistical laws, which describes the simplest possible mechanism of cellular differentiation. The nanometer scale, at which individual molecules move within cells, is ruled by chance. When we look at cells at that level, we can see the random motion of the molecules which somehow must occasionally come together to bring about chemical reactions. Those reactions are the basis of life itself: reading information from DNA, and using it to build molecules and cellular machinery. Cells are so small they may contain just a few molecules of a given protein, inherited randomly rather than equally during cell division. This random variation means that even in genetically identical cells, growing in the same environment, the information encoded in the same genes can be read and processed into proteins at different rates and intensities.



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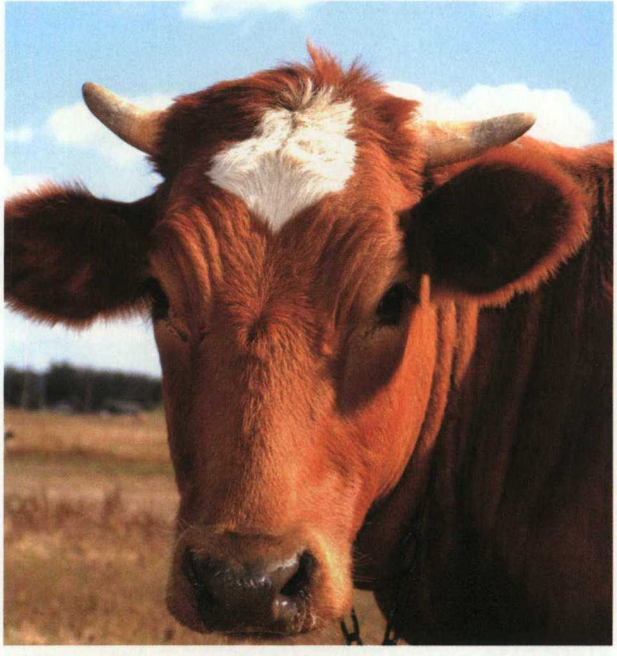
Yeast culture in Petri dishes

A statistical mechanism of evolution

What statistical laws are responsible for the fact that although on the nano level all chemical reactions are random, on the macromolecular level living organisms do perform highly complex and precise functions? One of the surprising features of living cells is the fact that they are able to take advantage of the statistical nature of the microscopic world for their own aims, and convert random chemical fluctuations into precise and ordered decision processes. This is why it is important to use statistical laws when describing gene regulation.

Genes are not everything

Our theory describes how a population of cells spontaneously divides into two groups that produce higher and lower levels of a certain protein (for example one providing antibiotic resistance). Even though cells in both groups have identical genes, the differentiation occurs purely due to random changes in the levels of transcription factors. These changes occur during cellular division and as a result of protein degradation. This phenomenon may be related to various genes. Although different genes encode different proteins, the mechanism of reading the code and producing these substances on this basis is basically the same. Bimodal gene expression occurs when cells differentiate without DNA mutations: under identical conditions, a group of cells spontaneously divides into two subgroups with higher and lower levels of gene expression. Certain types of this phenomenon may be responsible for cellular differentiation in genetically identical animals (monozygotic twins, clones), resulting in different phenotypes in spite of having an identical genotype.



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Higher organisms are systems comprising millions of cells – or miniature control elements. The more complex those systems are, the more capable they are of turning randomness into order

Our theoretical predictions are interesting because they reveal a certain non-intuitive phenomenon: even when cells form a single group, somewhat unclear in terms of the distribution of transcription factors, the population actually gets divided into two groups in terms of the amount of target proteins produced.

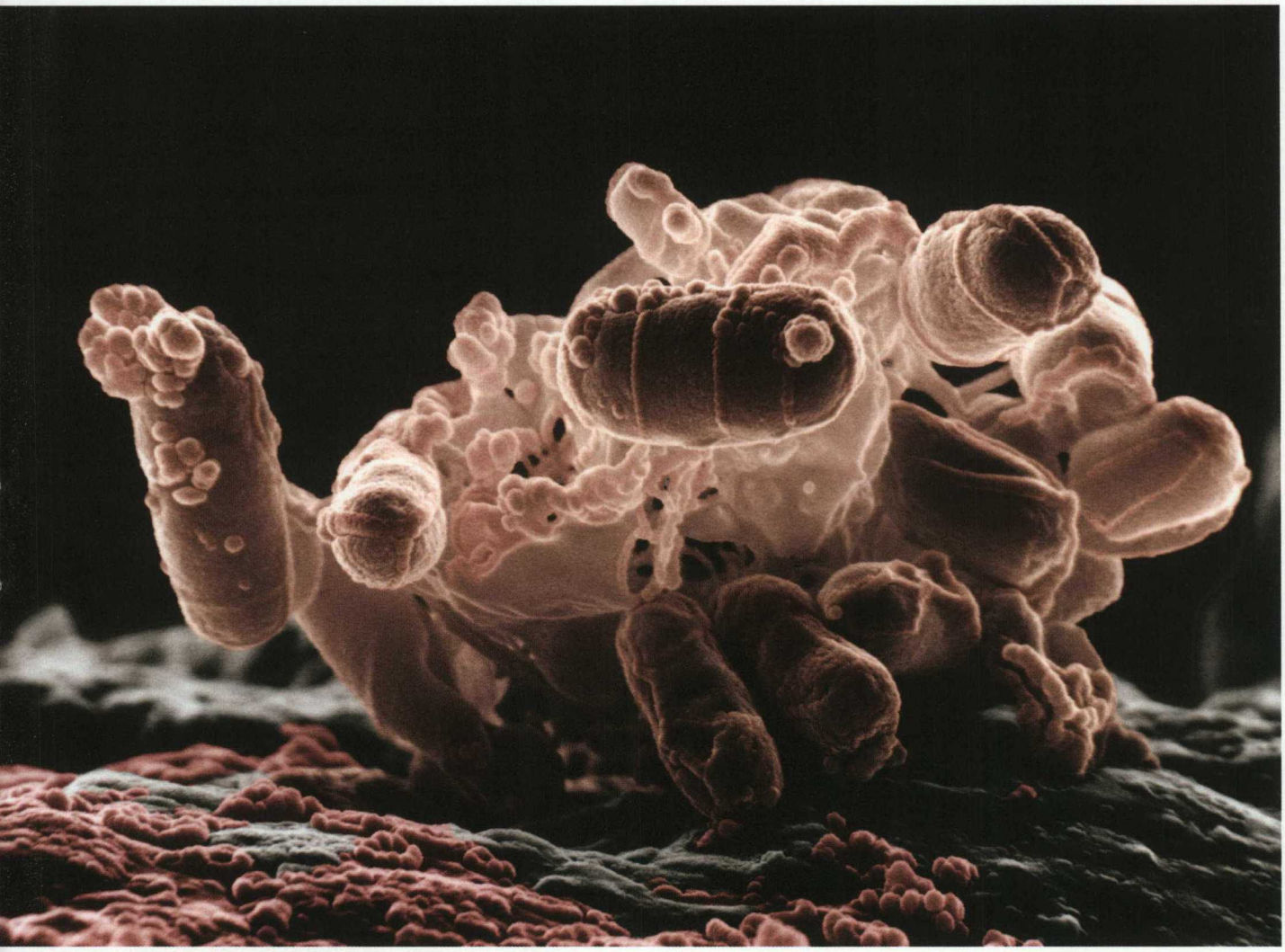
Bimodal expression mechanisms assume complex gene regulation: feedback when the protein product drives the activity of its own gene; slow folding or unfolding of DNA providing access to genes (known as chromatin remodeling); cooperative binding of several transcription factors; and multi-step gene regulation cascades.

In contrast with previous theories, we have shown that spontaneous cellular differentiation is theoretically possible without complex regulatory mechanisms. This happens when, as a result of cellular divisions, transcription factors have a specific statistical distribution in a population, concurrent to a typical biochemical scenario where gene activity is not directly proportional to the levels of transcription factors (in other words, when the gene expression is non-linear). This means that we have demonstrated the possibility of cellular differentiation on the level of the simplest possible gene regulatory system. Our research introduces an elegant method of theoretically predicting this type of bimodal gene expression without arduous calculations, using a simple geometric construction. This method may prove useful for researchers, since its application requires just a few experimentally-measurable parameters.

In search of a perfect strategy

Our innovative method provides a possible explanation for certain results of experiments on *E. coli* and yeast cells that have yet to be successfully interpreted: a qualitative change in the expression of the gene responsible for resistance to the antibiotic tetracycline. At low tetracycline concentrations, the cells form a single group where the resistance gene is inactive. At high concentrations they also form a single group, with the gene active in all the cells. However, at intermediate tetracycline concentrations, two groups arise spontaneously: one where the resistance gene is active, and the other where it is inactive.

This can be explained as a strategy similar to "portfolio diversification" when investing in a stock market in order to maximize gains and minimize risks. In order to survive in a changeable environment, the cells divide into two groups with high and low levels of expression of the given gene. This means they diversify their survival strategies: The group secreting the important protein has less energy to protect itself against adverse environmental conditions, but it proliferates more successfully. The cells in the inactive group, on the other hand,



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***E. coli* bacterial cells viewed through an electron microscope**

reproduce more slowly, but the energy so spared may aid survival in case of sudden environmental changes. In the mechanism we discovered, each cell remains at the same expression level throughout its cellular cycle. This is different from the dynamic bimodal gene expression that is found, for example, in chromatin remodeling, where each cell randomly switches over time, activating or blocking the expression of the gene. We suspect that the two different mechanisms of bimodal gene expression may be the result of adaptation to different types of environmental variation.

Systems biology has an enormous potential for innovation: it provides tools for biotechnology, which allows researchers to design genetic systems with the required properties. In turn, they have applications in medicine, pharmacy, agriculture, and various other industries.

So far our research has been carried out on the fundamental level; we have described a phenomenon which on the microscopic level simply amounts to lifeless chemistry, the motion of molecules subjected to random thermal forces. However, it is due to this seeming randomness that at a certain higher level cells seem to be able to make real life decisions, such as how best to adapt to the environment in order to maximize their chances of survival. Higher organisms are systems comprising millions such control elements, which transmit signals and form cascades and loops. It is likely that the more complex those systems are, the more capable they are of turning this randomness into order. During the days of early triumphs in the field of mechanics, scholars came to believe that living organisms are precisely-constructed machines. Today we know that mechanical determinism only manifests itself at the macroscopic level. When we probe deeper, however, we discover that in fact life is based on chance – but instead of destroying order, it actually creates it.

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Further reading:

Ochab-Marcinek A., Tabaka M. (2010). Bimodal gene expression in noncooperative regulatory systems. *PNAS, 107(51)*, 22096-22101.