PRODUCTION SYSTEMS OF THE BIOLOGICAL CELL

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Abstract: Biological cells are complex, sophisticated and very efficient production systems. They have survived and managed to evolve due to their abilities to adapt and to react promptly to environmental changes. The need to respond on changes on time, has resulted in a specific production system that uses small set of common building blocks that circulate in local recycling loops, and is able to add, remove or renew the needed "equipment" in a very short, critical time.

The paper proposes a framework for studying autonomous manufacturing systems, and under such a framework it develops a unified view toward unicellular organisms and autonomous manufacturing systems. It also proposes a conceptual model of autonomous manufacturing that covers both biological systems and human made FMSs, and restates the central dogma of genetics as central dogma of flexible manufacturing.

The knowledge that we have about these biological manufacturing systems could be used in building of the new generation of manufacturing systems. This paper is pointing out the analogies and some differences between the Flexible Manufacturing Systems (FMSs) and the production systems of the biological cell.

Keywords: Molecular genetics, Metaphors, Protein biosynthesis, Autonomous agents, Flexible manufacturing, Autonomous manufacturing

1 Introduction

Processes in molecular genetics are currently under intensive investigation. Although some mechanisms are understood to a level that they are not merely science but rather engineering, there are still processes that should be discovered and explained. RNA related problems, especially protein biosynthesis [23, 13] are among the problems that trigger scientists from different research fields.

In a scientific explanation, a very general methodology is the use of analogies and metaphors. We use knowledge from a known area in order to understand for ourselves or to explain to somebody else what is going on in the phenomenon under consideration. Molecular genetics is an example of area that uses analogies in explaining the observed phenomena.

2 Metaphors for Understanding Cell Processes

Various metaphors are currently used for understanding genetic information processing. Each of them has introduced its own concepts and terminology that is currently used molecular genetics. Our analysis recognizes the following metaphors:

Biochemistry Metaphor. The classical view into genetic processes is viewing them as biochemical reactions. This view named DNA and RNA after the fact that they are acids and they are found in the cell nucleus. Their constitutive elements were named nucleotides. A ribosome was named after the fact that it contains ribonucleic acid, RNA. This metaphor uses the concept of catalysis, a process of accelerating a chemical reaction by special types of proteins, named enzymes. Today biochemistry uses also concepts from other metaphors introduced later in the molecular biology research.

Linguistic Metaphor. This is the currently most widely used metaphor. The major contribution of this metaphor is the understanding that DNA is a string of letters, rather then just another acid [27]. The string contains information just like other written languages. The notions like transcription and translation were introduced by this metaphor, and are now basis of understanding the genetic information processing. The concept of genetic code [28] is a part of this metaphor as well. Revealing the complete string of letters for various DNA is now part of the genome informatics [10].

Factory Metaphor. This metaphor recognizes a ribosome as factory, assembly line for producing proteins [24]. This is a point of view that shows that the genetics system is not only about information processing. It is convenient to view it as a production process.

Flexible Manufacturing Metaphor. This metaphor proposes that DNA should be considered a database, rather the just a string of letters, and that a RNAs are programs for a flexible manufacturing process taking place in a cell. For example, mRNA is a program for making a product, tRNA is a program for transporting robots, and rRNA is a program for flexible assembly units, the ribosomes. This metaphor appeared [3, 4, 5] in the time when the RNA was discovered [9] to have also a catalytic role. This metaphor considers rRNA as an executable program, an active part of the ribosome, not just a glue to keep of the ribosomal proteins together. Later in 1991, it was shown that rRNA has indeed an active catalytic role [21], confirming the mentioned prediction of this approach. We believe that this approach is a part of the brave new RNA world [17, 14] effort. Within this metaphor the cell is considered as an integration of both information processing and material processing. Robotics terminology was introduced. A cell is viewed as an adaptive autonomous factory standing on some planet. These particular topics, symbiosis of material and information processing, robotics terminology and cell as an adaptive autonomous factory are of our interest, and will be exposed in more detail in the following text.

The FMS metaphor is currently accepted in some more classical views [2]. For example it is accepted hat DNA is a database, and that mRNA is a program for synthesis of a particular protein (or small number of proteins)

Systems Software Metaphor. This metaphor [7, 8] proposes that DNA is the cell Operating System, rather than just a cell database. The metaphor tries to understand the genetic information processing through the systems software "microscope".

3 Flexible Manufacturing Systems Metaphor

Flexible manufacturing systems [1] are main subject of interest of the modern manufacturing science. These systems are natural extension of the classical production systems after integration of the computers (CIM) [18, 19, 12] in the production process. The ability to encode a product in software and to use the CAD/CAM system in order to produce the designed product in a short time is the basis for flexible manufacturing. A FMS system can rapidly respond to an invoice or a market demand for a small quantity of product A, pipelined in a line that already carries a larger production demand of a product B. The concept of just-in-time (JIT) [16] is associated with the FMS paradigm, meaning that it is possible to organize a production in which all the supplies, even from external suppliers, are just in time of a need present at the right place. It is assumed that there is no need to keep a supply component in a factory warehouse "just-in-case"; the external supplier will deliver the required component just-in-time such that the ordered product will be delivered to the customer just-in-time.

There are many aspects of the flexible manufacturing systems studied in contemporary science and engineering [20, 25]. The knowledge obtained from these systems could be extended to a biological production system, the genetic mechanism of the protein biosynthesis. In the following text we further elaborate our view of the protein biosynthesis system as a flexible manufacturing system and point out some aspects useful for autonomous manufacturing systems.

Flexible manufacturing includes two important processing systems: material processing and information processing. Figure 1 shows the component of those systems emphasizing the analogies of both the systems within an FMS.

Figure 1 shows that at each level, the processing level, the transportation level, and the storage level, the material processing and the information processing have their equally important roles.

Studying the analogies between the artificial manufacturing systems and the manufacturing systems of the nature, we observe that the biological cell itself is an integration of information and material processing. In some cases, the boundary between the material and the information in the cell is not so obvious.

Studying the protein biosynthesis we also recognize two main flows toward a working ribosome: an mRNA flow containing information about the polypeptide chain that should be synthesized, and a tRNA flow carrying material, building blocks for the required protein [6]. We could also recognize the translation-I process as a material loading process, and the translation-II as a material transportation process (Figure 2).

Viewing the cell as a flexible manufacturing system, Figure 2 also gives a global view of its main processors. The main processing units for producing a single polypeptide chain are the transcriptase (RNA polymerase), the ARS-ase, and the ribosome. The transcriptases copy all the software required for producing a protein: the product description data (mRNA), the programs for automated guided vehicles (tRNA), and also programs (rRNA) for flexible manufacturing cells (ribosomes).

processing	information processors	material processors
transport	information transmission	material transportation
storage	information bases	material bases

Figure 1: FMS as integration of information processing and material processing

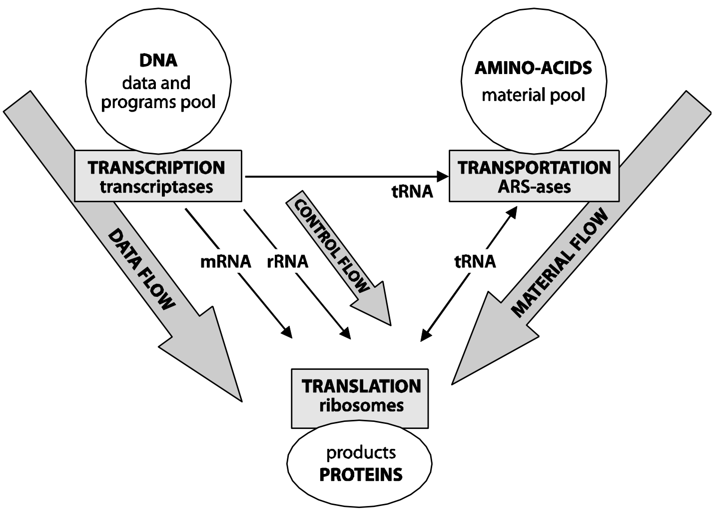

Figure 2: Information (control and data) flow and material flow in the cell FMS

The analogy to the ribosome in an FMS is a flexible manufacturing cell [22]. It receives programs (rRNA) and data (mRNA) to produce a protein. It has a sophistically programmed tertiary structure, on which there are designated sites where cell agents are received (for example, a special site for the tRNA's, a special site where translation termination proteins are received, as well as a specific site for attaching an amino acid to the protein chain). In eukaryotes the rRNA is produced in the nucleolus, where the components for the ribosomes are designed. In prokaryotes rRNA recognizes the binding site with mRNA (so called ribosome binding site or Shine-Delgarno sequence). With its tertiary structure it also has processing (catalytic) ability in the ribosomal complex.

There are two manufacturing systems in the cell: one for the basic systems and tools (carried out by the ribosomes), and the other for the final biochemical products (carried by the enzymes). The DNA has a role of the master database, which is read by an information accessing system (proteins that enable access and that perform operations with the database), and after that processed by an information processing system (operations on RNA). The whole process is governed by an event recognition and control system. The global control system including the database accessing system will be considered below.

All the produced components are present in the cell just-in-time for a next production step. The concept of just-in-time (JIT) production is an issue in human-made FMS [26]. Molecular genetics seems to be using that concept from the very beginning of the evolution. It seems that there is no specific storage area in the cell, just because there is no need for one. A goal of human made FMS, a "zero inventory" [15] system is achieved by biology to the extent it is possible. From the autonomous manufacturing viewpoint, it is important that the cell, as reaction to the environment, produces its machines just-in-time too, not merely products. It is what human made FMSs are still not doing. So, in building bionic manufacturing systems, building machines and other types of processors just-in-time when needed, is one step that should be achieved.

Considering the biological and human made manufacturing systems under the same framework, we now restate the central dogma of molecular genetics as a central dogma of flexible manufacturing. Figure 3 shows the new statement.

Instead of using terminology like transcription and translation, the terms information processing and material processing are used in Figure 3. The notions used in genetics like DNA, RNA polymerase, mRNA, rRNA, tRNA, ribosomes, and proteins are easily recognized. The revised statement shown on Figure 3 covers both the genetic manufacturing system, (protein biosynthesis), and human made manufacturing systems.

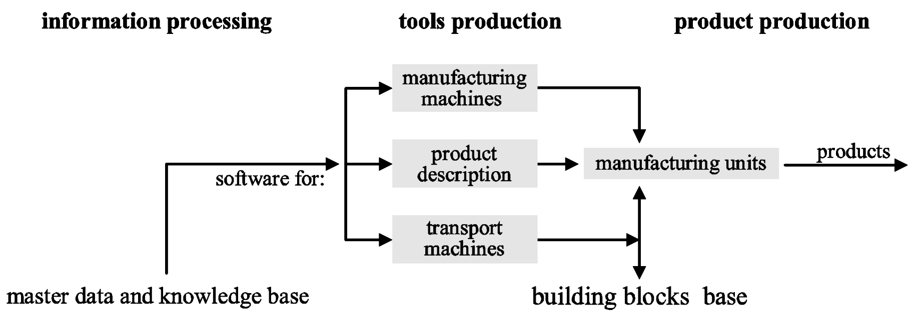

Figure 3: Central dogma of flexible manufacturing covering both biological and human made flexible manufacturing systems

4 Cell as an Autonomous Agent

On the basis of that concept which is here inferred from molecular genetics, we can infer a definition for *Autonomous Flexible Manufacturing System*: An autonomous

Flexible Manufacturing System is an autonomous system which, as an integration of information processing and material processing, is capable in a certain period of time of producing a subset of products from its repertoire of possible products, and is capable of changing its production subset or the whole repertoire due to a change in the environment it exists in. Concepts such as self-repairing and self-reproducing systems can also be defined as extensions of this definition.

The framework of our study bases on the observation that the biological cell is an agent existing in an environment in which it behaves (e.g. moves), and it manufactures some products for itself and also for the environment (Figure 4).

The cell can be an active autonomous agent, an example being the bacterium Escherichia coli, or can have a more passive role as a specialized worker in a multicellular system, an example being a cell of the human skin. In both cases the cell receives signals from the environment including signals from other cellular agents, and responds to the signals. The cell has special sensors for various signals, and some of the cells have motors which allow them to move in the environment.

During its life, the cell has two principal responses to environment changes, a behavioral response and a product manufacturing response. The cell has also a type of response that deals with both reproduction and termination of its life as reaction to the environment change.

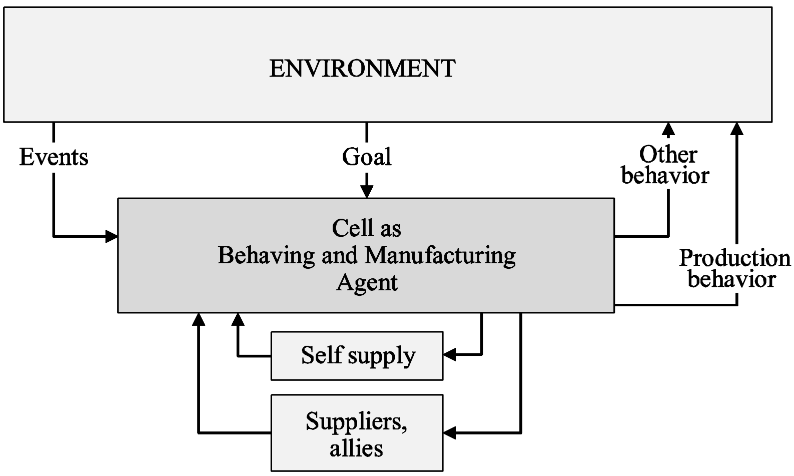

Figure 4: The cell as an agent interacting with its environment

5 Cell Material Processing

The cell is a masterpiece in material processing. It uses a small set of basic materials to produce variety of cell components. Four nucleotides, twenty amino acids, some saccharides and fatty acids are the basic building blocks that are used for the synthesis of major cell molecules: DNA, proteins, polysaccharides and lipids, respectively. A second, lower level of commonality is found in the central metabolism. Here, a limited number of about 30 intermediates can be identified, which serve as precursors for the above-mentioned nucleotides, amino acids, saccharides and fatty acids and many other biomolecules. Moreover, the intermediates used for producing goods and for producing machines (enzymes) are identical in a biological cell. In other words, the cell can easily degrade an enzyme into its component amino acids and use these amino acids to synthesize a new enzyme, possibly a job doing machine. It seems an amazing achievement for the cell to build the complexity and variety of life with such a small number of components.

The cell's modular approach allows it to perform some very astonishing procedures. It enables it to regulate and maintain capacity, respond to external changes and recycle its components in ways that we can only dream of in today's manufacturing systems.

As production technologies become more advanced, manufacturing may see a similar convergence around a common set of versatile materials. Increasing parts commonality is on the rise in industry, but at a very rudimentary level [11].

The cell's metabolic pathways are designed in such a way that different end products often share a set of initial common steps. For example, in the biosynthesis of aromatic amino acids, a number of common precursors are synthesized before the pathway splits up for different final products. This commonality reduces the number of enzymes needed to synthesize amino acids, thus conserving energy and building blocks. It postpones the decision of which amino acid, and how much of it to synthesize. Another striking example of commonality is steroids, a class of common molecules in microorganisms, plants and animals. Steroids help in performing various biological functions, such as regulation (hormones) or solubilization of fat (bile acids). Their basic structure is a sterane skeleton, which is modified by side chains and functional groups that give the particular molecule its specific biological activity. Steroids perfectly match the industrial definition of a platform – a set of subsystems and interfaces that form a common structure from which a stream of derivative products can be efficiently developed.

6 Discussion and Conclusion

The flexible manufacturing metaphor is one of the metaphors that try to explain the flow of the material and processes that happen in the biological cell. When it emerged, in the eighties, it gave possible explanation of the roles of the tRNA (as a shuttle, a mobile robot that carries its load, an amino acid), the aaRS-ase was easy to recognize as a loading station for the automated guided vehicles (AGVs). The ribosome was recognized as a flexible manufacturing cell with unload station for AGVs. The FMS approach recognized the DNA as a cell database, which now seems to be an accepted terminology. However, we would argue that the most striking result of our approach so far is the proposed role of the rRNA molecule in the process. The FMS approach proposed it as a program for the ribosome, and in fact the protein biosynthesis in ribosomes is a rRNA driven process.

Going a step beyond the flexible manufacturing metaphor, this paper considers the autonomous flexible manufacturing system as a surviving, adaptive system, and studies the analogy to unicellular production systems, such as bacteria. It proposes a unified framework for studying autonomous manufacturing systems in which the agent behaves in an competitive environment, produces products for such a changing environment, produces product for its own reparation and survival, and communicates to potential suppliers. Basing on the observation of the bacteria behavior, the need of social communication can be understood as a need of allies to survive in an environment.

The cell has developed an effective way to produce its products and machines. It uses common building blocks, and it recycles them. This enables it to build needed tools and products just in time, and so it has very small and ever changing inventory. This concept of "just-in-time" production, and "zero inventory" is what material scientist experts strive to achieve with the human made production systems. Therefore, exploration and intensive study of biological cells can lead to better efficiency of tomorrow production systems.

7 References

1. A. Arbel, A. Seidman, Performance evaluation of flexible manufacturing systems. IEEE Trans. Systems, Man, and Cybenetics , 1984
2. S. Bolsover, J. Hyams, S. Jones, E. Shephard, H. White From Genes to Cells. Willey-Liss, 1997
3. S. Bozinovski. "Flexible manufacturing systems: A biocybernetic approach" In M. Vukobratovic, E. Popov (Ed.) Proc Symp on Robotics and Flexible Manufacturing, Moskow, 1986, p. 192-197
4. S. Bozinovski. "Mobile robots in flexible manufacturing systems" (In Serbo-Croatian) Proc Conf ETAN, Bled, p. 409-415, 1987
5. S. Bozinovski, L. Bozinovska, "Flexible production lines in genetics: A model of the protein biosynthesis process", Proceedings of the International Symposium on Robotics, Dubrovnik, 1987.p. 1-4
6. S. Bozinovski "Neuro-genetic agents, genetic code, and flexible manufacturing metaphor" CMPSCI Technical Report 96-01, Computer Science Department, University of Massachusetts at Amherst, 1996
7. S. Bozinovski, B. Mueller, F. diPrimio "Biomimetic autonomous factories" GMD Report 115, German National Research Center for Information Technology, Sankt Augustin, 2000
8. S. Bozinovski, G. Jovancevski, N. Bozinovska "DNA as a Real Time Database Operating System", Proceedings of the World Multiconference on systemics, Cybernetics and Informatics, Vol 15, 65-70, 2001
9. T. Cech, B. Bass. "Biological catalysis by RNA", Ann. Rev. Biochemistry 55: 599-629, 1986

10. N. Cooper (Ed.) The Human Genome Project, University Sciences Books, Mill Valey, CA, 1994.
11. L. Demeester, K. Eichler, C. Loch. Organic production systems: What the biological cell can teach us about the future of manufacturing. INSEAD Working Paper Series, 1993
12. A. Engel "Beyond CIM: Bionic manufacturing systems in Japan" IEEE Expert, 79-81, August 1990
13. E. Gardner, P. Snustand, Principles of Genetics, John Wiley and Sons, 1984.
14. M. Gray, R. Cedergren "The new age of RNA", FASEB Journal 7 , 1993
15. R. Hall. Zero Invertory. Dow Jones-Irvin, 1983
16. A. Hernandez, Just-in-Time Manufacturing, Prentice-Hall, 1989.
17. M. Hoffman, "Brave new (RNA) world", Science 254: 389-389, 1991
18. A. Kochan, D. Cowan. Implementing CIM, Springer, 1986
19. D. Koenig, Computer Integrated Manufacturing, Hemisphere Publishing Corporation, 1990.
20. A. Naylor, M. Maletz. "The manufacturing game: A formal approach to manufacturing software" IEEE Trans Systems, Man and Cybernetics 16: 321-334, 1986
21. H. Noller, "Ribosomal RNA and translation," Annual Review of Biochemistry 60: 191, 1991.
22. M. Ptashne. "How gene activators work" Scientific American, 41-47, 1989
23. V. Ratner, Control Systems in Molecular Genetics, (In Russian) Nauka, Novosibirsk, 1975.
24. I. Rosenfield, E. Ziff, B. van Loon, DNA for Beginners, Writers and Readers, 1984.
25. N. Slack, " Manufacturing systems flexibility –An assessment procedure" Computer Integrated manufacturing Systems 1: 25-31, 1988
26. R. Stassey, C. McNair. Crossroads: A JIT success story. Dow Jones-Irvin, 1990
27. J. Watson, F. Crick A structure of the deoxyribose nucleic acid, Nature 171: 737-738, 1953
28. C. Woese, The Genetic Code, Harper & Row, New York, 1967.