LIFE CYCLES AND COMPETITION IN MODELLING OF ARTIFICIAL AND BIOLOGICAL CONTROL SYSTEM

Ivars Mozga
Uldis Grunde-Zeiferts
Sandis Sudars
Egils Stalidzans
Biosystems Group, Faculty of Information Technology,
Latvia University of Agriculture,
Liela iela 2, LV 3001, Jelgava
Latvia
ivars.m@gmail.com

KEYWORDS
Biological control system, life cycle, competition.

ABSTRACT

The modelling of control loops within functioning biological organisms is a prerequisite for a successful treatment or therapy development and implementation in biological systems. Similarities in emergence and sequential lifecycle steps of human made artificial control systems (ACS) and natural biological control systems (BCS) in multigeneration scale are analysed and compared to extract additional knowledge for modelling procedures.
The development of ACS includes: 1) definition of targets, 2) design of control system, 3) execution of control system, 4) behaviour of technical object as observable result, 5) feedback to the design.
The development of BCS has appropriate steps in different execution and includes: 1) predefined targets (survival and reproduction), 2) genome (as design of control system), 3) cells and organism (as execution of biological control system), 4) behaviour of biological object as observable result, 5) feedback to genome (as design of control system).
The differences and common features in execution principles of each step in both lifecycles are discussed. Consequences of ACS and BCS lifecycle joining in case of artificial control of biological system are discussed.
Perspectives of Systems Biology as emerging science about modelling of biological processes regarding modelling of BCS are mentioned.

INTRODUCTION

Historically the control theory first arose out of a need to understand the behavior of systems. This theory was then used to design and engineer better systems. It is not difficult to foresee that, in biology, control theory may follow the same path (Ingalls et al. 2006). The effect prediction and the analysis of control system implementation becomes complicated in case of biological object of interest: it has own control loops and competition of several loops of object and designed control system can occur. An understanding of dynamic behaviour of biological object is important forecasting consequences of any interaction with it. In the new science Systems Biology (SB) behaviour of biological system can be analysed as expression of genetically coded control system of an organism (Alberghina and Westerhoff 2005, Ingalls et al. 2006, Klipp et al. 2006).
Holistic approach based quantitative model of a biological object or process becomes a tool that can either confirm or deny new hypotheses about elements and interactions of a functioning biological system as model and its original (biological object) can be compared in dynamic behaviour. Validated model can become a tool for intensive experiments before implementation of a control or therapy under most critical circumstances taking into account transition processes.
In multigeneration evolutionary scale the development of technical and biological systems has similarities and differences in strategies and means of execution.
The goal of this paper is to analyse differences and similarities in evolutionary lifecycles in scale of many generations of biological objects as natural biological control systems and human made artificial control systems. Joint life cycles in case of controlled biological object have to be analysed. Control analysis related possibilities of Systems Biology as a new biosystem modelling approach have to be analysed.

DEFINITIONS

An artificial control system (ACS) is a human designed control system. It can be executed by technical, chemical, biological or other means. By ACS in this paper is meant very wide range of control systems for example simple technical control system (climate control system in a building), complex technical control system (control system of an aircraft), human made control system of biological objects (fermentation process control), human designed control of biological object by another biological object (pest control by purposeful introduction of their biological enemies).
A biological control system (BCS) is in biological reproduction process developed control system that ensures internal processes within biological object and interaction processes with environment. Features of biological objects are metabolism and reproduction. BCS controlled biological objects are for example all living organisms (plants, animals, humans) as well as their subsystems (body temperature control, metabolism, processes within a cell).
There are different definitions of Systems Biology (SB) available indicating different accents of SB mission:

- SB research behaviour and interactions of elements in functioning biological system (Palsson 2000, Ideker et al. 2001).
- SB can be defined as understanding of complex biological systems integrating experimental and computational research (Kitano, 2002).
- SB studies how properties of live forms arise from interaction of their components (Reiss 2005).

Systems biology approaches comprise (Reiss 2005):

- The enumeration of network and pathway components in complex biological contexts,
- The reconstruction and mathematical modelling of networks, pathways or living systems,
- The mathematical representation of networks based on quantitative biological datasets,

The mathematical analysis and simulation of networks to assess their properties and biological experiments to verify or falsify mathematical models of biological systems.

ACS AND BCS LIFECYCLES

Successful ACS and BCS have to fulfil the goal of control. ACS is made by humans and therefore the lifecycle of successful control system is well defined. Experience and common sense set rational sequence of operations.
The lifecycle of ACS and BCS consist of operations with similar meaning executed by completely different methods and means (Figure 1).

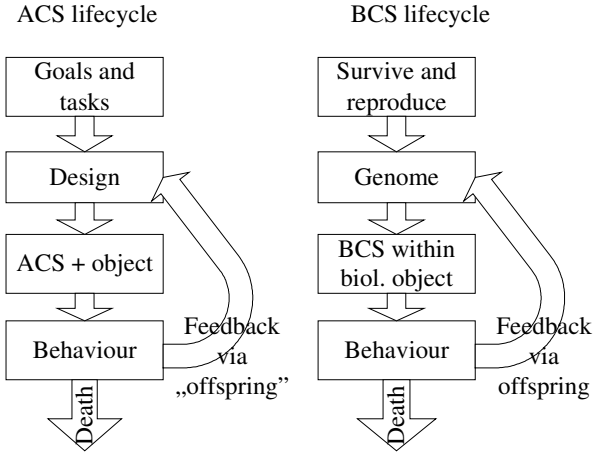

Figure 1. Life cycle of ACS and BCS.

Goal setting

The first stage of ACS lifecycle is the setting of control goal by developers of system - humans. Different tasks can be set to reach goals: stability, safety, efficiency and others.
The first stage of BCS lifecycle – setting of goals and targets - takes place without humans. Still there are two targets that are common for all biological objects: reproduction and survival as there is no other way to continue evolution and other criteria's become less important in multigeneration scale.

Design

The second stage of ACS lifecycle is the development of a design to reach the tasks. The design usually is based on some of the best previous generation designs that have to be more or less improved accordingly to collected experience.
The second stage of BCS lifecycle ends by next generation organism design: genome (Klipp et al. 2006) represented as a set of DNA double helix. That is a form of design record that contains all the necessary information to build a biological system. A incremental development of genome takes place in iterations with one generation step. The base of the new genome is the combination of parent genomes that have proven ability to survive and reproduce. The next iteration of a genome is modified by crossover and mutations thus providing flexibility of next generation. A set of the BCS (genome) of every specie of biological organism is recorded by the same means – a DNA molecule thus indicating enormous potential of this form of record.

Implementation

ACS has to be built accordingly its design. Often the object to be controlled is an autonomous system and ACS is a separate unit. Build-up of ACS usually is modular. Ready modules are interconnected until stage when system can function.
The implementation of BCS design is automatic reproduction of cells the way as it is set in the genome. BCS develop simultaneously with the biological object (from system of several cells to complete organism) to be controlled and has to control the system during different development stages where different modules develop from stem cells. In case of BCS it is usually impossible to split the object and BCS.

Behaviour

The behaviour of the ACS in a technical system should correspond to the planned dynamic behaviour. ACS has high repeatability: Properly functioning ACS behaves the same way if circumstances stay the same. Complicated control system often needs fine-tuning or some not automated adjustments.
The genome defines BCS behaviour in all its complexity. Even flexibility is encoded in the genome as it does not change during a lifetime of a single organism. Some control loops of BCS that are responsible for internal processes in biological object act since birth through different growth stages of biological object. Parents and specific circumstances of the environment tune later some other loops (conditional reflexes) of BCS that are responsible for interactions with environment where the biological object has to fulfil its targets – survive and reproduce. This kind of flexibility enables adaptation of biological object where it is necessary. BCS has low repeatability: BCS may behave different even if circumstances stay the same.

Feedback

The fine-tuning and some adjustments as described earlier in the item "Behaviour" may be part of multigeneration level behaviour of ACS and BCS.
ACS is successful if the goal of implementation is reached. Then ACS should be copied (reproduced) accordingly previous successful design creating a batch of ACS as a "offspring". The design might be slightly corrected for specific circumstances if they are known in advance. In the case of un-

successful ACS design can be radically changed in one generation step using other means or (and) structure of ACS.
BCS is successful if readiness for reproduction is reached and an offspring is produced. Otherwise the genome (design) of BCS will not be repeated in the next generation. The research in genetics gives overview of genome repeatability in the next generation (Klipp et al. 2006). Actually it is not repeating. The crossover and mutations create a variety of BCS offspring preparing designs of BCS for possibly changing circumstances. Still the main part of offspring is almost a copy of successful previous generation. Mutations take care of extremes in the new generation. That is a strategy that allows being ready for unpredictable environment changes, which are even not experienced by previous generation. Still the feedback of successful parents is a strong guideline.

ARTIFICIAL CONTROL OF BIOLOGICAL OBJECTS

The interest about biological objects and processes if often caused by a wish to control them (change their behaviour). Control of biological system without artificial changing BCS (genome) can be executed by a modification of environmental parameters of the biological object. BCS as a set of control loops will react to changes in the environment. The knowledge about reaction rules of BCS (including dynamics) to environmental changes is the key to ACS design. If the goal of ACS implementation is a specific behaviour of biological object it is necessary to know which environmental parameters can cause it. ACS has to be designed to ensure the necessary environment.
ACS can be optimised accordingly efficiency criteria (costs, safety, environmental friendliness) if there is more than one set of environmental parameters that cause needed behaviour of BCS.
Thus the development of efficient ACS of a biological object is closely related to the BCS. Lifecycles of ACS and BCS (Figure 1) have to come together into a unit "artificially controlled biological object" (Figure 2). Assuming that we can not change BCS lifecycle, the one of ACS has to be adapted.
Several significant changes take place (Figure 2):

1. Two control systems: BCS and ACS are working in parallel. They interact and compete via one or several environmental parameters. Transition processes (Weyrick 1975, Stalidzans 2005; Stalidzans and Markovitch 2005a,b; Dorf and Bishop 2005) become critical. Only ACS can be modified to ensure safe control process. This kind of task can be solved by the methods of control theory if both control systems are described mathematically by differential equations. That can be done for ACS as it is human made system. Quantitative mathematical description of BCS is problematic as its design (genome) is not human made and the list of system components is not sufficient without description of their interactions. The quantitative description of BCS dynamics is a huge reverse engineering problem where SB offer new approaches and methods trying to combine dynamic experiments of behaviour with DNA-encoded design elements of BCS. The current stage of SB does not offer complete BCS model of even smallest and simplest cell. Still often model of a part of the process of interest is highly valuable.

2. Feedback loop of BCS is changed. Within the feedback loop "Genome", "BCS within biological object" and "Behaviour" the node "BCS within biological object" is changed by interaction with ACS forming new node "ACS+BCS within biological object". As a result in next generation's better reproduction rate will get the biological objects, which are the best for environment modified by ACS. Thus genome (design of BCS) via feedback will shift from optimal behaviour in the environment towards optimal behaviour in the environment changed by ACS. This fact brings potential danger: will biological object survive if ACS is removed and the changed genome (ACS impact) will have to fulfil survival and reproduction target in historical (without ACS) environment?

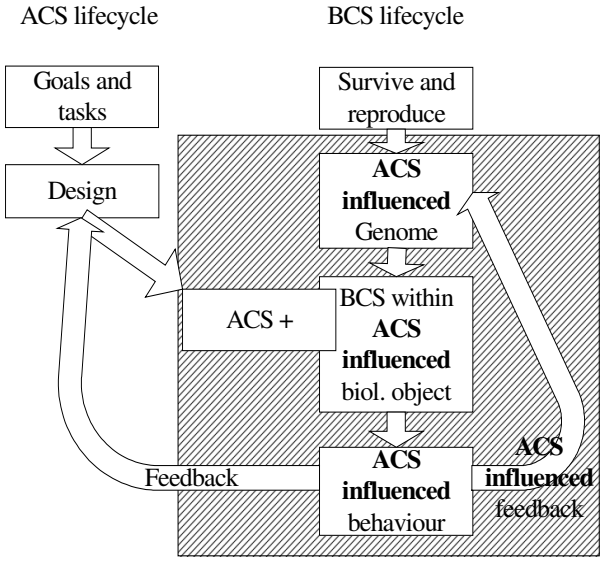

Figure 2. Lifecycle of meld ACS and BCS during control of biological objects. Colored area is impacted process of BCS cycle.

3. A new feedback loop "Design", "ACS+BCS within biological object" and "Behaviour" has developed. Thus design of ACS can be improved taking into account human made and predictable ACS and hardly predictable nature product BCS. The hardly predictable BCS cause hardly predictable behaviour as well as its feedback to the design. Thus ACS lifecycle has to be more adaptive to stay effective in next "generation" of ACS.

4. Overlapping of feedback loops mentioned in items 2 and 3. Both loops have two common nodes: "ACS+BCS within biological object" and "Behaviour". Two feedback loops improve their performance at the same time accordingly the node "behaviour". This is another competition of ACS and BCS taking place in different time scale compared to the competition in dynamics described in item 1). Control system design competition (design in case of ACS and genome in case of BCS) takes place in long term – many generations of ACS and BCS development. Also there transition processes are possible because of competition but it takes place in respectively slow speed. Accordingly to control theory adaptivity of ACS design has to be quicker than the one of genome to take lead in this competition.

PERSPECTIVES OF SYSTEMS BIOLOGY (SB)

The representation of biological models in form of differential equations used in SB is the necessary precondition in use of control theory to describe BCS (regulatory networks in SB) the same way as ACS. Thus SB can contribute in control development of biological objects (Ingalls et al. 2006). Some directions of SB and other related sciences like bioinformatics aim to describe evolutionary process allowing analysis of biological objects in multigeneration scale as well measuring intensity of mutations and crossover and their effects on evolution.

Currently SB is mainly focussing on simulation of biomolecular processes within and between cells that are building blocks of any living organism. This knowledge has to be used in quantitative modelling of genetic, subcellular, cellular, tissue, organ, and system structures (Noble, 2006) that very often are targets of biological object control.

CONCLUSIONS

The differences in evolutionary lifecycles in scale of many generations of biological objects as natural biological control systems and human made artificial control systems are found mainly in means of their execution while the function of feedback loop has many similarities.

The development of ACS includes 1) definition of targets, 2) design of control system, 3) execution of control system, 4) behaviour of technical object as observable result, 5) feedback to the design. The development of BCS has appropriate steps in different execution and include 1) predefined targets (survival and reproduction), 2) genome (as design of control system), 3) cells and organism (as execution of biological control system), 4) behaviour of biological object as observable result, 5) feedback to genome (as design of control system).

Lifecycles of ACS and BCS partially meld in case of artificial control of biological object. Following new effects take place: 1) two control systems (ACS and BCS) act in parallel as some of their loops cross and transition process has to be taken into account, 2) feedback loop of BCS is changed, 3) feedback loop of ACS is changed, 4) feedback loops in ACS and BCS lifecycles overlap. Melding of ACS and BCS development lifecycles cause evolutionary shift in genome that has to be compensated changing ACS.

The new science Systems Biology aims to describe behaviour of BCS controlled biological systems in form of quantitative dynamic models. This approach allows application of automatic control theory for ACS development and optimisation of ACS and BCS collaboration leading to improvement of control development for biological processes.

REFERENCES

Alberghina L., Westerhoff H. (Ed.) (2005) Systems Biology: Definitions and Perspectives, Springer, 408p.

Dorf R.C., Bishop R.H. (2005). Modern Control Systems, Tenth edition. Pearson Education , Inc. Pearson Prentice Hall. 634 p.

Ideker T., Thorsson V., Ranish J.A. et al. (2001) Integrated genomics and proteomic analyses of a systematically perturbed metabolic network. In: Science 292, pp.929-934.

Ingalls B.P., Yi T., Iglesias P.A. (2006) Using Control Theory to Study Biology. In book System Modeling in Cellular Biology, Ed. By Zoltan Szallasi, Jorg Stelling and Vippul Periwal, Massachusetts Institute of Technology. 243-267.

Kitano H. (2002) Computational systems biology, Nature 420, pp.206-210.

Klipp E., Herwig R., Kowald A., Wierling C., Lehrach H. (2006). Systems Biology in Practice. Concepts, Inplementation and Application. WILEY-VCH Verlag GmbH&Co KgaA. 465 p.

Noble D. (2006) Multilevel Modeling in Systems Biology: From Cells to Whole Organs. In book System Modeling in Cellular Biology, Ed. By Zoltan Szallasi, Jorg Stelling and Vippul Periwal, Massachusetts Institute of Technology. 297-312.

Palsson B. (2000) The challenges of in silico biology. In: Nature Biotechnology 18, pp.1147-1150.

Reiss T. (2005) Workpackage 1: International Benchmarking and foresight of systems Biology. The Take-off of European Systems Biology (EUSYSBIO). Karlsruhe, Germany, 44 p.

Stalidzans E. (2005). "Algorithms of computer control of multiobject biological systems." PhD thesis. Riga Technical University, Riga, p. 156.

Stalidzans E., Z. Markovitch (2005 a) "Methodology of control system development for biological systems under information insufficiency". In European Modelling Simulation Symposium EMSS 2005, Marseille, France, 20-22.October 2005. pp.169-175.

Stalidzans E., Z. Markovitch (2005 b). "Development of dynamic model for a biological system under conditions of insufficient information". In Proceedings of ITAFE'05 International Congress on Information Technology in Agriculture, Food and Environment, Adana, Turkey October 12-14, 2005, pp. 337-344.

Weyrick, Robert C. (1975) Fundamentals of automatic control. New York: McGraw-Hill, 397 p.

AUTHOR BIOGRAPHY

IVARS MOZGA studied IT in Latvia University of Agriculture. Since 2006 he is a PhD student in Latvia University of Agriculture specializing in computer control of biological systems. Doctoral studies are connected to modeling of biomolecular processes within cellular structures.

ULDIS GRUNDE-ZEIFERTS studied Information Technologies in Latvia University of Agriculture. Since 2006 he is a PhD student and lecturer in Latvia University of Agriculture specializing in computer control of biological systems. He is mainly interested in recognition of biological control loops and their parameters.

SANDIS SUDARS studied IT in Latvia University of Agriculture defending masters thesis in 2007. Mainly interested in modeling technologies of technical and biological systems and software development.

EGILS STALIDZANS studied in Riga Technical University (Latvia), Faculty of Computer Science and Information Technology where defended his PhD in 2005. Research is mainly related to development of mathematical models under information insufficiency. In 2007 he became assistant professor and senior researcher at Latvia University of Agriculture, Faculty of Information technology. Since 2006 he leads Biosystems Group. He is interested in application of Systems Biology approach in control of industrial bioprocesses.