

NiSIS Task Force 'Nature Inspired Monitoring and Control'

Survey on Information Flow in Biosystems

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A Introduction

The goal of the Task Force 'Nature Inspired Monitoring and Control' is to compile relevant biological control principles and to present them to Information and Communication Technology (ICT) experts to assess their potential for Applications in ICT. Microbial cells represent the smallest viable cellular unit.

Depending on environmental conditions they are able to perform highly complex processes such as growth, self-reproduction and/ or even dormancy. The cellular metabolism consists of a set of approximately 2000 biochemical reactions by which substrates are degraded to gain energy and to form small molecules which in turn are utilized to build up complex molecules with highly specific functions and structures. The principles by which cellular processes are controlled and coordinated represent tailor made model systems for the design of complex control tasks in many other areas of life. Cells have developed complex hierarchically organized regulatory networks to manage the spatial and temporal coordination of the individual information fluxes to provide the appropriate amount of each metabolite and to cope with nutrient starvation or other perturbations. Some of these features, such as network architectures, modularisation and hierarchical structures, have already been transferred to ICT. However the continuous advancement of life sciences, in particular the analytical capabilities of high-throughput technological platforms provide the means to decipher novel principles to be further explored and exploited in ICT. Potential topics in this context are repair mechanisms, multifunctionality of proteins, spatial compartementation, spatial domain – function relationship, signal processing, etc.

Bacteria like *Escherichia coli* have “known” for millions of years on how to digest their food. Otherwise they would not be alive any more. Men started only recently, in the postgenomic era, understanding bacterial metabolism. But both bacteria and men need not understand their own metabolism to keep alive (at least in some healthiness). However, men must understand the foreign metabolism of bacteria to take influence on it and to manage it to men's benefit.

Bacteria do not really “know” how to metabolise: they just do it, just like men do. Nevertheless, men speak about cells as intelligent information–handling systems and about information flow in cells and biosystems. This is of course an anthropomorphic metaphor. What is meant by this manner of speaking is just human understanding of cellular metabolic processes and control to get capable of exploiting them in an optimised fashion.

Of particular interest in this context is genetic manipulation of bacterial cultures in biotechnology where bacteria are exposed to athropogene stress by forcing them to produce foreign proteins.

B Key Elements of Cellular Regulation and Control [1]

Due to their complexity, cells have evolved multiple regulatory networks to control metabolism, growth and replication. Hierarchical organisation, modularisation, redundancy by development of alternative pathways and feedback control circuits are mentioned as key elements, mechanism and strategies to achieve both adaptability and robustness. The key

elements of (transcriptional) regulation of prokaryotes are shown in Table 1: Sigma-factors, transcription factors; regulatory strategies, such as two-component regulatory systems (phosphorylation/dephosphorylation), regulatory motifs and models; definition of robustness, basis mechanisms that confer robustness to biological and engineered systems. Analytical platforms providing insights on molecular level will improve the monitoring of individual components and thereby facilitate comprehension of their interplay.

The cellular regulation is characterized by modular construction and the repeated use of similar biochemical and genetic modules at the different hierarchical levels, such as promoters, operators, repressors and activators, which reappear in global control and even in intercellular communication mechanisms.

To keep cells alive their metabolic networks have to cope with environmental perturbations of different kinds. Examples are milieu or temperature shock, nutrient supply or deprivation or conditions of starvation. This requires cellular adaptation to exogene and endogene perturbations. A particular perturbation affects cells in bacterial cultures of fermentation in biotechnology, which are forced to produce foreign proteins by their secondary metabolism, as discussed in the following chapter.

Tab. 1
Key elements of the regulation of gene expression

Name	Description of the natural phenomenon	For more information see Chapter in [1]
Regulation	Transcription control by operons controlled by repressors/activators. Expressed proteins: biocatalysis, binding, structure. RNA- polymerase (RNAP) catalyses transcription, specificity for promoter sites by sigma factors at RNAP	18 Regulation of Gene Expression: Operons and Regulons 25 Sporulation and Cell Differentiation: sigma factors
Sigma factors	Complex metabolic control by sigma factors, able to recognize different promoter consensus sequences and bind to RNA to trigger specific expression. Particular perturbations trigger specific sigma factors in hierarchical regulatory networks of signal transduction.	28 Adaptation to Extreme Environments: sigma factors for different environmental perturbations
Regulatory strategies	Levels of metabolic control: transcription, mRNA stability, translation substrate uptake, biomolecule structure. Complex regulatory and signalling networks to maintain growth and overcome perturbations. "master regulators", "housekeeping genes"	30 Ecophysiology and Ecological Niches of Prokaryotes: metabolic capacity, substrate usage, metabolic adaptation 21 Regulation of Fermentation and Respiration: sensory and regulatory networks involved in the control of corresponding genes
Two component regulatory systems	Phosphorylation/dephosphorylation of regulatory protein by effector molecules in signal transduction, as transcription switch.	20 Global Regulatory Networks and Signal Transduction Pathways: two component systems, adaptation strategies
Regulatory motifs and modules	Motifs: small regulatory subnetworks in clusters of function, structure etc. analogous to switches, amplitude filters, oscillators, noise filters, amplifiers, logic	18 Regulation of Gene Expression: Operons and Regulons: operon, regulon, modulon, stimulon

	gates, and memory units. Moduls: interconnected motifs	
Robustness of cellular functions	Definition of robustness. Maintenance of function in spite of perturbation, or canalisation towards a specific outcome from uncertain input conditions. Function or outcome needs to be specified since in complex systems increase of robustness of one feature can render other features more fragile	28 Adaptation to Extreme Environments: bacteria have the capacity to withstand extreme environmental changes and can adapt quickly. Their adaptive strategies are directed towards survival rather than growth. 30 Ecophysiology and Ecological Niches of Prokaryotes: 31 Habitats of Prokaryotes: environmental perturbations are substrate limitation, fluctuating conditions, light-darkness, oceans or soil, temperature, pH
Mechanisms conferring robustness to biological and engineered systems	Redundancy, feedback control, hierarchy, modularity, developmental control circuits. Redundancy is versatility of pathways, Modularity: functional units with strong internal connections. Hierarchy: different layers of integration of subsystems in specific control tasks. Cellular networks are hierarchically organized and provide sophisticated design. Developmental control circuits: multi-cellular systems provide increased robustness due to specialization of different cells	Section III Diversity of Metabolic Pathways 19 Posttranslational Control and Modification of Proteins: allosteric control, feedback inhibition, feedforward activation, phosphorylation, protein compartmentalization, Section V Gene Expression and Regulatory mechanisms: Modularity, Hierarchy 25 Sporulation and Cell Differentiation: cellular differentiation and multicellular development

C Monitoring Cellular Metabolism in Recombinant *Escherichia coli* Cultivations

For achieving high quantities of recombinant protein strong host/vector systems are utilized. The use of such strong host/vector systems quickly leads to an overburden of the host cell metabolism. Thereby the endogenous nutrient starvation of the bacterial host is triggered which may even lead to a metabolic collapse within a short time after inducing recombinant gene expression. Severe stress can also lead to increased heterogeneity of the target protein. To confer increased resistance cells have evolved complex regulatory networks acting on highest level of metabolic regulation, such as the stringent response (i.e., a translational control mechanism of prokaryotes that represses tRNA and rRNA synthesis during amino acid starvation).

In order to ensure the required stability of the process, screening and evaluation of signals triggered by cellular stress response represent an essential requirement for the implementation of an advanced monitoring concept. Signal molecules of regulatory networks, like sigma factors and Guanosine-Tetra-Phosphate (ppGpp), enable the expression of specific genes and proteins in response to strong recombinant protein production. The spatiotemporally coordinated expression of specific genes plays an essential role in the overcome of adverse conditions.

The transcriptional network of *E. coli* is the best known but by far not completely understood among the currently used host organisms. Although the regulatory network is very complex, comprising of 4405 identified open reading frames insight is provided by its hierarchical organization. Tight control of gene expression is effectuated by a low number of global

regulators, like the transcription factors Crp, FNR, IHF, FIS, ArcA, NarL and Lrp regulating 51% of genes in *E. coli*. In addition seven different sigma factors are involved in genetic regulatory networks, which are induced due to different environmental conditions. Furthermore, sRNAs and low molecular weight effector molecules, like cAMP, ppGpp and autoinducers, participate also in stress acquisition and regulation. The combination of these regulatory components enables the fine-tuning of the stress response networks and consequently an immediate reaction on changes of physiological and environmental conditions by induction of specific genes.

D Cellular Dynamics and Information Flow [2, 3]

Biological systems like cells process physical substrates and information. Metabolic reactions consume and produce substrates, e.g. for building of cell structures or gain of energy. Getting stimuli from outside, cells regulate these mechanisms. They process and integrate this information with their state, e.g. by passing the information into the nucleus and regulating gene expression by transcription factors, yielding a changed physical behaviour of the cells.

A growing number of studies elucidates the behaviour of smaller subsets of the extensive signalling networks of a cell. These smaller subsets may for example be a signalling cascade initiating the production of a certain gene of interest. So-called "upstream" processing and proteins moderate the occurrence and properties of a gene. Then, the gene itself moderates its "downstream" processing, genes and proteins.

Signal transduction at the cellular level refers to the transfer of signals from outside the cell to inside. The transfer of signals can be simple, like that associated with receptor molecules of the acetylcholine class: receptors that constitute channels which, upon ligand interaction, allow signals to be passed in the form of small ion movement, either into or out of the cell. These ion movements result in changes in the electrical potential of the cells that, in turn, propagates the signal along the cell. More complex signal transduction involves the coupling of ligand-receptor interactions to many intracellular events. These events include phosphorylations by tyrosine kinases and/or serine/threonine kinases. Protein phosphorylations change enzyme activities and protein conformations. The eventual outcome is an alteration in cellular activity and changes in the program of genes expressed within the responding cells.

Signal transducing receptors are of three general classes [4]:

1. Receptors that penetrate the plasma membrane and have intrinsic enzymatic activity
Receptors that have intrinsic enzymatic activities include those that are tyrosine kinases (e.g. PDGF, insulin, EGF and FGF receptors), tyrosine phosphatases (e.g. CD45 [cluster determinant-45] protein of T cells and macrophages), guanylate cyclases (e.g. natriuretic peptide receptors) and serine/threonine kinases (e.g. activin and TGF- β receptors). Receptors with intrinsic tyrosine kinase activity are capable of autophosphorylation as well as phosphorylation of other substrates.

Additionally, several families of receptors lack intrinsic enzyme activity, yet are coupled to intracellular tyrosine kinases by direct protein-protein interactions (see below).

2. Receptors that are coupled, inside the cell, to GTP-binding and hydrolyzing proteins (termed G-proteins). Receptors of the class that interact with G-proteins all have a structure that is characterized by 7 transmembrane spanning domains. These receptors are termed *serpentine* receptors. Examples of this class are the adrenergic receptors, odorant receptors, and certain hormone receptors (e.g. glucagon, angiotensin, vasopressin and bradykinin).

3. Receptors that are found intracellularly and upon ligand binding migrate to the nucleus where the ligand-receptor complex directly affects gene transcription.

A cell senses stimuli and hormones by the binding of these substrates to its specific receptors. The receptors undergo a conformational change or form complexes, thus translocating the information of the stimuli into the cell interior. Intracellular receptor domains then mediate the conformational changes of the receptor to the intracellular environment (e.g. by autophosphorylation of receptors in the intracellular part). Adaptor and anchor proteins are situated at the inner plasma membrane of cells, which are receiving these signals by biochemical or binding modifications. Then they carry the signal into the cytoplasm and nucleus of the cell, by diffusion, by interacting with other signal molecules or by regulating diffusion spikes of secondary messengers (small substrates like Ca^{2+} or cAMP). Normally the strength of the signal is amplified in the cytoplasm by a cascade of biochemical interacting signal molecules. These interacting proteins build a network of interaction, one interaction influencing one or several other interactions.

Signalling is mediated by biochemical changes in signal molecules. These changes are the basic blocks for signal transduction in the cell. The signal transduction itself must then be seen as a chain or network of such biochemical changes, whereby the change in an enzymatic activity of a protein, upstream in the signal pathway, is influencing a downstream protein by a biochemical reaction.

Chains become networks when bifurcation takes place:

proteinA → proteinB → proteinC
proteinB → proteinD.

Regulation of pathways is done by positive and negative feedback loops:

e.g. proteinC increasing the activity of proteinA (positive feedback),
proteinC → proteinA
or proteinD decreasing the activity of proteinA (negative feedback).
proteinD ⊣ proteinA

The information flow through the network is massive parallel. Networks result from interconnections between signaling pathways (so-called crosstalk between different signaling pathways). Such interconnections occur because the same signaling component is capable of receiving signals from multiple inputs. Such networking may occur within similar classes of signaling pathways, such as between the Ras and Rho pathways, and between different pathways, such as the Gs/cAMP and MAP kinase pathways. There are two general classes of interconnections: junctions, which are signal integrators and nodes, which split the signal and route them to multiple outputs. An immediate complexity that arises from these definitions is that they are not mutually exclusive properties for signaling components.

An early example of signal integrators was adenylyl cyclase, which was shown to produce cAMP in response to signals from Gs-coupled receptors as well as Ca^{2+} . As adenylyl cyclases were cloned and characterized, it became obvious that the different isoforms were capable of receiving signals from a wide variety of inputs and thus cAMP levels in the cell could serve as an indicator of the balance of signals between many pathways. Additionally, from junctions signals may be routed to regulate numerous physiological events, as is the case with protein kinase A. The adenylyl cyclases-cAMP-PKA module is a junction at the adenylyl cyclase end and a node at the protein kinase A end.

Signal integration at junctions can be both positive and negative. Raf, serving as a junction between the MAP kinase and cAMP pathways, best exemplifies this. Here, opposite types of connections are observed when different isoforms of Raf are present. c-Raf is inhibited by protein kinase A while B-Raf is stimulated by the cAMP pathway. Thus, to understand signal integration at this junction, the molecular identity and relative proportions of the junctional components need to be known. This type of knowledge about concentrations of various cellular components in the natural context will be quite important for the development of accurate models of signaling networks.

Networks also contain nodes where signals may be split and routed through several different pathways to regulate distinct cellular functions. Like junctions, nodes may also be upstream or downstream in the network. One of the best upstream examples of a node is the receptor tyrosine kinases, which can route growth factor signals through many different pathways. Although such routing can result in regulation of multiple independent cellular functions (e.g., growth factors), signal routing through multiple pathways can produce combinatorial signal specificity at the level of gene expression. Such combinatorial specificity may be used as a mechanism to establish hierarchy amongst the regulated cellular processes.

A downstream example of a node is Cdc42, a member of the Rho family of GTPases. It receives signals from many receptor pathways and in turn can regulate a number of different cell functions through regulation of different effectors. The capability of a network component such as Cdc42 (or another Rho-related GTPase) to regulate a number of different cellular processes endows the network with the ability to regulate multiple cellular tasks.

A general mechanism used for the assembly of signaling networks is the formation of complexes of signaling proteins. The organization of these complexes is dynamic and the complexes are often assembled in response to signal input. One of the more noteworthy aspects of these signaling complexes is the number of proteins that are organized together.

It appears possible that there may exist a general intracellular signaling network in diverse cell types. Of course the inputs and outputs are different. The extracellular signal input in the case of the neuron is the diffusible neurotransmitter glutamate and in the case of the T cell are cell–cell interactions with the antigen-presenting cell. The receptors are different as well, but nevertheless they engage a similar intracellular signaling network. The physiological outputs are cell type–specific: in the case of the neuron there is a change in the excitatory postsynaptic potential and in the case of T cells there is the secretion of IL-2. However, the cellular machinery such as the movement apparatus as well as the transcriptional and translational apparatus engaged by the signaling network is the same. It is also noteworthy that many of the components in the T cell and neuronal networks are also found in networks that transmit proliferative signals, giving credence to the idea that there is a general signaling network in diverse cell types.

The molecular mechanisms by which the signaling complexes are organized are beginning to emerge. As with many other general signaling concepts, the cAMP pathway provided some of the earliest evidence for the role of anchoring proteins (AKAPs) in the assembly of signaling complexes and in providing a spatial dimension to signaling. AKAPs are multivalent and bind a number of protein kinases and phosphatases to form signaling complexes that should have the intrinsic capability to both consolidate and dissipate biochemical signals. AKAPs themselves are targeted to distinct regions of the cell. Therefore, the cell has the means to assemble signaling complexes at specified locations in an activity-dependent manner.

A general theme that emerges from the study of the various classes of scaffolding proteins is that these proteins possess bidirectional specificity. At one end they specifically recognize one or a group of signaling components and at the other end a location within the cell, thus providing the molecular basis for spatial organization of signaling pathways. Bidirectional specificity itself is a general mechanism for routing signals. Heterotrimeric G protein α subunits couple to selective classes of receptors and specific effectors and thus provide specificity in linear signal transfer. Mechanisms of signal transfer such as binding of phosphotyrosine residues to PTB domains are also used as scaffold assembly mechanisms. Such assembly using signal transfer mechanisms is not restricted to scaffold proteins alone. Effectors themselves, functioning as scaffolds, can use this mechanism to assemble signaling complexes in order to regulate the timing of signal flow.

Although there are a large number of components and interactions, the studies with the scaffolding proteins allow us to reach the following conclusions about the assembly of signal

networks. Scaffolds are the building blocks onto which signaling nodes and junctions are assembled. Such assembly provides a natural mechanism to achieve selective separation of signaling components and thus achieve specificity of signal routing. The scaffolds also provide a mechanism by which signals can be spatially resolved within the cell and thus provide the spatial dimension to signaling networks. Since interactions between components in the signaling complexes can be regulated by signal inputs, a unique feature of biological signaling networks is that junctions and nodes can be assembled and disassembled in an activity-dependent manner. This property sets biological signaling networks apart from physical networks where network architecture is preset and cannot be reorganized by signal input. The molecular complementarity between interacting partners and the spatial constraints provided by the anchors, scaffolds, and other organizing centers provide the physio-chemical basis for activity-dependent self-organization as a unique emergent property of biological signaling networks

A major function of signaling networks is to place a value on the signal such that it is either converted into further biochemical event and subsequently a biological response or safely dissipated within the network. The signal can come from a single input such as Ca^{2+} in the postsynaptic region, where it can activate many signaling pathways that comprise a network, or from multiple inputs, each of which individually activates one or more signaling pathways within the network. The issue is how can the signal within the network be evaluated such that the appropriate physiological response is mounted. Generally, when signals are of sufficient amplitude for a specified duration, they evoke a physiological response and such signals can be considered consolidated signals. In the laboratory the simplest way to obtain a consolidated signal is to provide a high-amplitude (pharmacological dose) extracellular signal for an extended period. Although this approach has been very useful in tracking the linear signaling pathways, it is not reflective of physiological situations. Here, extracellular signals are generally subsaturating and often pulsatile in nature. How are these signals consolidated? Consolidation depends on network architecture and the regulatory mechanisms such architecture provides. Most linear signaling pathways themselves have a variety of mechanisms to dissipate signals at various levels of signal flow. At the receptor level the process of desensitization can rapidly limit signal flow. This type of regulation is seen in heterotrimeric G protein pathways, where receptor kinases (GRKs) rapidly uncouple the receptors from the G proteins. Receptors can also be downregulated (i.e., removed from the site of action), although this mechanism is slower and most often used to limit the effect of subsequent stimuli.

The second locus of regulation to achieve signal consolidation is at the level of signal transducers. In both small and large G protein pathways, the duration of the activated state of the G protein determines the amplitude and duration of signal flow. Persistent activation of G proteins by inhibition of the intrinsic GTPase activities has profound physiological and pathophysiological consequences. Inhibition of the GTPase activity of $\text{Gs}\alpha$ by cholera toxin leads to inhibition of water reabsorption in the intestine and consequently dysentery, a major symptom in cholera. Similarly, mutations that inhibit the GTPase activity of Ras are associated with a significant portion of human tumors. There are a large number of proteins that regulate the GTPase activities of both small and large G proteins. These GTPase activating proteins are called GAPs for small G proteins and RGS proteins for the heterotrimeric G proteins. A common feature between both small and heterotrimeric G protein pathways is that both the amplitude and duration of signal propagation beyond the G protein is regulated by the relationship between the receptor signal and the regulation of G protein activity. Since the G protein regulators themselves may be regulated through the network, signal consolidation at the level of G proteins is a network property. Additionally, interactions between the GAPs may result in junctions between the signaling pathways.

The third major locus of signal consolidation is at the level of protein kinases. Persistently activated protein kinases are capable of triggering physiological functions. Examples abound, including persistently activated protein kinase A in cholera, persistently (mutationally)

activated tyrosine kinases and MAP kinases in proliferation and neoplastic transformation, and persistently activated calcium-calmodulin kinase II in long-term potentiation of synaptic responses. Often these key protein kinases are activated by phosphorylation in response to upstream signals. The duration of activation of the key protein kinase is determined by the balance of signal input and the phosphatases that limit the amplitude and duration of the activated protein kinase. Alternatively, sequential inhibitory phosphorylation by protein kinases from other pathways can also regulate signal consolidation. Such gating interactions involving protein kinases and phosphatases form one class of junctions in the assembly of signaling networks. Since anchors such as AKAPs bring together protein kinases and phosphatases, it is not only the interactions but also the organization of the network that determines whether a given signal will be consolidated at the level of protein kinases to obtain a physiological response.

The mechanisms of signal consolidation described above result in two emergent properties of the network. The first is the setting of threshold for the physiological response. Thresholds can be set at multiple levels and are dependent on the concentration of the signaling components, interactions between the components, and the colocalization of the interacting components. Thus, selective movement of the consolidated signal (i.e., either an activated protein kinase such as MAP kinase or an activator such as cAMP) to the appropriate location could function as a mechanism to set local thresholds for the conversion of biochemical reactions into physiological responses. The second system property that emerges from signal consolidation is the ability to propagate responses across different time scales. The distribution of consolidated signals to different cellular locations where they can stay active for various lengths of time could be one mechanism by which signals can be used to regulate physiological responses that depend on the integrated functioning of several cellular machines and that operate over different time scales.

Consolidated signals produce changes in cellular functions. Many mammalian cells respond to extracellular signals with changes in a number of cellular functions, and it is the combination of these altered functions that constitutes the physiological response. For example, stimulation of the CA1 glutamatergic neuron can result in an immediate increase in synaptic efficiency ([24]), dendritic outgrowths, stimulation of local protein synthesis, altered patterns of gene expression, biochemical remodeling of the synapse, and persistent changes in synaptic efficiency. Similarly, in the case of immune responses, the T cell moves toward and contacts the antigen-presenting cell, alters patterns of gene expression and eventually secretes cytokines. In both cell-types each function is executed by distinct cellular machinery that is located in a defined region within the cell. How are these functions regulated in a spatially and temporally coordinated manner? The signaling network will integrate the function of these machines to produce the physiological response. Here the cell may be considered analogous to a chemical plant with a number of reactors. The overall control system for the plant (i.e., the signaling network) will ensure that the different reactors function in a coordinated manner such that raw materials (corresponding to extracellular signals) introduced into the chemical plant results in the appropriate products (corresponding to changed physiological functions) at the output. We should be careful to limit this analogy since the architecture of the chemical plants (reactors and control system) is fixed while the architecture of the signaling networks and even some of the cellular machines is constantly changing. This analogy does raise the issue of how engineering design principles may be used to develop a function-based understanding of signaling networks and their regulation of cellular machines.

More than 50 cell signaling pathways are visualized in [5]. The UCSD-Nature Signaling Gateway is a comprehensive and up-to-the-minute resource for anyone interested in signal transduction [6]. This Gateway represents a unique collaboration between the University of California San Diego (UCSD) and Nature Publishing Group and is designed to facilitate navigation of the complex world of research into cellular signaling.

The signal of the sensed stimulus gets translated into a cell reaction by alteration of gene transcription in the cell nucleus. This is done by the influence of signal molecules on transcription factors (TF). TFs control gene expression by binding to transcription sites of genes and therefore changing the binding ability of polymerases responsible for gene transcription (TFBS – Transcription factor binding sites). TF and TFBS form networks of gene regulation [7]. But also regulation without changing of gene transcription takes place, directly altering the enzyme activity of effectors, which take part in metabolic reactions and therefore changing the substrate (metabolism) concentration in cells.

The cellular metabolism is the way to digest and store nutrition, grow, defend against external attacks like heat, hunger stress or nutrition changes. These reactions are moderated by the quantity and efficiency of the metabolites (substrates) and the metabolic enzymes which enable the reactions. For example, glucose is digested by hexokinase into glucose-6-phosphate, being the educt for the next reaction, that yields fructose-6-phosphate and so on. These reactions are the basis for a metabolic petri-net, consisting of alternating nodes of enzymes and metabolites. Additionally, the regulation of the metabolism may be modulated by signalling molecules. Metabolic reactions and networks are well studied and accessible via publicly available databases (e.g. KEGG [8], Brenda [9]). Further, many enzymes exist in measurable amounts in the cell and hence can be used for quantitative investigations.

Currently available and novel techniques in genomics, proteomics, and life cell imaging are applied to generate high quality quantitative data under standardized conditions. In an iterative process experimental design are being used to generate data that facilitate detailed dynamic pathway modeling.

Cellular information processing requires the coordinated activity of a large network of intracellular signalling pathways. Crosstalk between pathways provides for complex non-linear responses to combinations of stimuli. A global analysis of cross-talk suggests that many external stimuli converge on a relatively small number of interaction mechanisms to provide for context-dependent signaling [10].

The overall goal of the Alliance for Cellular Signaling [11] is to understand as completely as possible the relationships between sets of inputs and outputs in signaling cells that vary both temporally and spatially. The same goal, stated from a slightly different perspective, is to understand fully how cells interpret signals in a context-dependent manner. This will involve identification of all the proteins that comprise the various signaling systems, the assessment of time-dependent information flow through the systems in both normal and pathological states, and finally the reduction of the mass of detailed data into a set of interacting theoretical models that describe cellular signaling.

E Nature Inspired Monitoring and Control [12, 13]

Today's information infrastructure, e.g. internet, mobile communications and e-commerce, is a global complex system that consists of great numbers of local interacting components, a system that is so complicated and dynamic that centralized hierarchical control is generally not an option. To be able to competently operate in and fruitfully contribute to this infrastructure, one must engineer systems that are able to adapt to the environmental uncertainty and the failure or replacement of its components, without direct human intervention.

An attractive approach to meeting this challenge is to utilize the principle of self-organizing in the living nature with its local-to-global emergence. This approach is based on the idea that rich and complex global properties can emerge from purely local interaction between agents. Such systems generate order via self-organization, self-regulation, self-repair and self-maintenance and no global or central organizer is required. However, when designing a

system that is based only on local interactions and the emergent properties resulting from these interactions, it is a difficult research problem to characterize the global behavior of the system as a whole. Self organizing applications (SOAs) should be based on such an analysis and understanding. For example, typical examples of SOAs are systems that reproduce socially-based insect behavior, such as ants-based systems, artificial life, or robots. Current developments are focused on Bio-inspired process algebra, approaches to handling local/global agent behavior, approaches to handling robustness, scalability, efficiency and maintenance in self-organising applications, performance engineering of emergent behavior in multi agent-based systems. To tackle the challenge of self-diagnosing and self-healing automation systems the ICT system must meet the requirements and provide the necessary support to implement for example model-based diagnostics, fault prediction tools and decision support tools. It is also envisioned that an ICT system must be self-diagnosing and self-healing to provide the necessary robustness [13].

There are several running initiatives in systems biology that could support the development of nature-inspired ICT, e.g. the "Virtual Cell Project" (<http://www.nrcam.uchc.edu>) and the E-Cell Project (<http://www.e-cell.org/>).

References

- [1] Lengeler, J.W., Drews, G., Schlegel, H. (1999): *Biology of the Prokaryotes*. Georg Thieme Verlag, Stuttgart.
- [2] Weismüller, M., König, R., Eils, R. (2002). Modelling of information flow in cells, Proceedings of the 16th European Simulation Multiconference, Darmstadt, June 3-5, pp 413-417; www.dkfz-heidelberg.de/tbi/people/koenig/documents/paperESM2002.pdf
- [3] Jordan, J.D., Landau, E.M., Iyengar, R. (2000): Signaling Networks: The Origins of Cellular Multitasking'. *Cell*, 103, 193–200.
- [4] <http://web.indstate.edu/thcme/mwking/signal-transduction.html>
- [5] www.sigmaaldrich.com/Area_of_Interest/Life_Science/Cell_Signaling/Pathway_Slides_and_Charts.html
- [6] <http://www.signaling-gateway.org/>
- [7] Schacherer, F., Choi, C., Götze, U., Krull, M., Pistor, S., Wingender, E. (2001): The TRANSPATH Signal Transduction Database: a Knowledge Base on Signal Transduction Networks'. *Bioinformatics*, 17, 1053–1057.
- [8] Kanehisa, M., Goto, S. (2000): KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic Acids Research*, 28, 27–30.
- [9] Schomburg I., Chang, A., Schomburg, D. (2002): BRENDA, enzyme data and metabolic information. *Nucleic Acids Research*, 30,47–49.
- [10] Natarajan, M., Sternweis, P.C., Lin, K.M. Hsueh, R.C., Ranganathan, R. (2006): A global analysis of cross-talk in a mammalian cellular signalling network. *Nat Cell Biol*, 8, 571-80.
- [11] <http://www.afcs.org/>
- [12] <http://esoa.altarum.net/esoa06/>
- [13] http://ec.europa.eu/information_society/istevent/2006/cf/network-detail.cfm?id=836