Establishing the hierarchies in regulation

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in time

Vacancies: 2 postdoctoral fellows for:

BBSRC funded research project for 2 postdocs (3 year each) with one technical assistent (2 year)

Location: Manchester Cnetre for Integrative Systems Biology, Manchester Interdisciplinary BioCentre, the University of Manchester

Supervisors: Hans V. Westerhoff, Douglas B. Kell, Stephen G. Oliver, Barbara M Bakker (Amsterdam)

Information: hans.westerhoff [at] manchester.ac.uk

Background

Distributed control is understood

In living organisms macromolecules invariably occur in networks. Most often the functioning of these molecules is not determined by their own physical chemical properties alone, but also by the properties of other molecules in the network (Westerhoff, 2005). A well-known case in point is that of the control ('limitation') of the rates at which enzymes function in metabolic pathways at steady state. Control of those rates tends to be distributed over the enzymes (Groen et al., 1982). *Molecular* systems biology analyzes how the biological system around molecules affects their functioning. Networks of living cells are part of a democratic hierarchy (Westerhoff et al., 1990) and the actual flux through a step in a metabolic pathway may be controlled not only by the properties of other enzymes in that pathway or by the transporter into that pathway (Bakker et al., 1999) but also by the activity of the transcription process, by properties of the ribosomes, by the topological state of the DNA (Snoep et al., 2002), etc. Similarly, transcription is not only controlled by RNA polymerase but also by cellular processes that determine the level of transcription regulators such as cAMP. Hierarchical Control Analysis has shown that also in this case control can be distributed and much control of the functioning of an enzyme tends to reside outside the properties of that enzyme (Snoep et al., 2002).

Distributed regulation is not yet understood

Approaches such as metabolic and hierarchical control analysis and biochemical systems analysis help quantify which properties of the intracellular networks *control* intracellular processes, also for time-dependent systems (Peletier et al., 2003, Hornberg et al., 2005). The word "control" is herewith used in the sense of limitation. It addresses the extent to which a cellular process would accelerate if a property of the intracellular network were activated. It does not address *regulation*, i.e. whether that property is actually activated when the cell adapts to a different condition. For instance, it does address whether activation of hexokinase would have the effect of increasing the steady state flux through glycolysis, but it does not address the issue whether hexokinase is actually being activated (*e.g.* through increased transcription of its gene) when yeast is shifted from aerobic to anaerobic conditions.

Yet, understanding how a living cell actually *regulates* the activities of its macromolecules is one of the important issues of biology. In cases where the transcription rate of a certain gene is regulated by a cell when it senses the presence of a different nutrient, the cell may accomplish this in various ways. It may increase the activity of its RNA polymerase, it may increase the concentration of one of the transcription factors, or of a metabolite that binds to that transcription factor, or it may change its chromatin structure. Evidence on the involvement of one such factor is often extrapolated as indicating the involvement of only that regulatory pathway. When the engagement of two such factors is reported by different groups, it is often supposed that one of the two groups must be 'wrong'. However, (just like control; see above) regulation can involve multiple mechanisms in parallel. It has been a problem to decide how one could validate this when indicators of regulation were only qualitative, *i.e.* in

the sense that a mechanism could only be involved or not involved, not 'half involved'. **The approach we wish to develop aims at making it possible to deal with regulation quantitatively.**

An important concrete case of this issue is to what extent metabolic fluxes are regulated by gene expression and to what extent by metabolic processes. According to one paradigm, metabolic fluxes are regulated through transcription activation or repression. An orthogonal paradigm only considers metabolic regulation. How could one deal with this apparent paradox experimentally? And, could one examine whether one of the two mechanisms is always dominant, or if not, when the one is dominant and when the other? Or, could one perhaps subtly establish the relative importance of the two types of regulatory mechanism for various conditions and various enzymes?

Regulation analysis for between steady states

We elaborated an approach (Ter Kuile & Westerhoff, 2001; Rossell et al., 2005), called regulation analysis (not to be confounded with control analysis, cf. above) that enables one to discriminate between metabolic and gene-expression regulation. The idea is as follows. Because enzymes serve as catalysts (and not here as substrates) of reactions, enzyme rate equations are usually of the shape:

$$v = V_{\max} \cdot f(S, P, X, K_S, K_P, K_X, ...) \qquad (1)$$

Here, v is the rate, S, P, and X represent the concentrations of the substrate(s), products(s), and coenzymes/other allosteric modifiers of the activity of the enzyme, respectively. K_S, K_P, K_X, represent the Michaelis-type constants for substrate product and other factors, respectively. … refers to other parameters that characterize the kinetic mechanism. V_{max} , i.e. the maximal forward rate of the step in the pathway, is equal to the concentration of the enzyme, e, times the catalytic rate constant, k_{cat}. Thus, $f(S,P,P,X,K_S,K_P,K_X,….)$ refers to a (reduced) rate equation, which, incidentally, is a difference between two rational polynomials with the same denominator.

When conditions change, the rate at which this enzyme operates may change; it is being regulated by the organism to some other, probably more appropriate, magnitude. Our approach is simple: the rate may be regulated through changes in the concentration of enzyme (*i.e.* through e hence V_{max}) or through changes in any of the other factors. We associate the former type of regulation with gene-expression regulation or 'hierarchical regulation'. We refer to the latter type of regulation as 'metabolic regulation' (even though some of it may be set in motion by gene-expression regulation of other enzymes, it reaches the enzyme under study through <u>metabolic</u> changes).

In order to determine the extent to which regulation is exerted through gene expression, we determine both the change in rate of the reaction catalyzed by that enzyme and the change in enzyme concentration experimentally. When the enzyme concentration has increased by the same factor as the steady state flux has, we conclude that regulation has run completely through gene expression. When the enzyme concentration has not changed at all, we conclude that it was entirely metabolic regulation. More interesting are perhaps the intermediate cases, in which some regulation is through gene expression and the rest is via metabolism. This is resolved by looking at how much of the percentage change in flux can be explained by the measured percentage change in enzyme concentration. The actual procedure is a little bit more precise: we divide the logarithm of the change in enzyme concentration by the logarithm of the change in steady state flux and the result is the fraction of the regulation that is through gene expression:

$$1 = \frac{\Delta \log V_{\max}}{\Delta \log J} + \frac{\Delta \log(f(S, P, X, K_S, K_P, K_X, ...))}{\Delta \log J} \equiv \rho_h + \rho_m \qquad (2)$$

The last part of the equation defines the gene expression (ρ_h) and the metabolic (ρ_m) regulation coefficients. Δ refers to the change (which can be quite large; unlike control analysis, regulation analysis is not limited to small changes to be exact). In the rare cases where the environmental change that is at the origin of the adaptation of the organism directly affects the enzyme under study, there is an additional term in the equation, i.e., the immediate response coefficient, ρ_i.) Our method has been applied to well-managed steady states, *e.g.* to Trypanosomes cultured in chemostat (Ter Kuile & Westerhoff, 2001), to corynebacteria (Chassagnole et al., 2003), and to the regulation of glucose transport activity in yeast (Rossell et al., 2005). The results showed that regulation induced by varying substrate limitation was accomplished both metabolically and through gene expression, to relative extents that varied with conditions and type of regulation. This proved that in living cells regulation is likely to be subtle.

Now the next step: Analyzing the dynamics and the hierarchies of regulation

What the above regulation analysis has not yet done however is to reveal how the living cell brings about subtle regulation. We surmise that (i) the cell has rapid regulatory mechanisms on stand-by, which it immediately brings to

bear once the environmental change occurs. We expect that (ii) the early mechanisms are different and perhaps less in efficiency and effectiveness as compared to the late mechanisms. Hence we should expect that (iii) the initial regulatory mechanisms are replaced by other more effective mechanisms; this process might repeat itself a couple of times. For this reason it is important to perform regulation analysis not only looking at the difference between the initial and the final steady state, but to do it throughout the transition between the initial and the final steady state. Such time-dependent regulation analysis should reveal whether and how the cell deals with changes in terms of a succession of mechanisms in time. We further hypothesize that (iv) for external challenges that may have occurred also in its evolutionary history, the sequel of regulatory mechanisms is optimal in the sense of bringing to the front the most effective/efficient mechanism that can be achieved in view of the kinetic limitations; in this vein we guess that metabolic regulation will precede posttranslational enzyme modification, which will precede transcriptional/translational regulation. In view of this fourth hypothesis we shall have to perform the time-dependent regulation analysis not only with sufficient temporal resolution, but also with a sufficient resolution of the various levels of the cellular regulation hierarchy, such as transcription, translation, posttranslational modification and metabolic regulation. **This is exactly what we shall do in this research project.**

Preliminary work

In order to develop the time-dependent regulation analysis experimentally, we need one experimental system in which already at steady state, regulation is distributed between gene-expression regulation and metabolic regulation, and a regulatory transition the organism has been confronted with in its evolutionary history. Moreover, it should be possible to measure the flux through a number of enzymes that are of interest in terms of the regulation of their activity. In addition it should be possible to determine the activity of the same enzymes, and, in view of the interest in the hierarchical regulation, also the concentration of the enzymes and of the mRNAs encoding them. *S. cerevisiae* undergoing starvation for carbon or nitrogen after a period of relative affluence, is a suitable model system from this perspective. We all have extensive experience with this organism and one of us (SGO) has made a preliminary study of the impact of starvation on gene expression in *S. cerevisiae* (Wu et al., 2004) whereas another one of us (HVW) has made such a study *vis-à-vis* the impact in flux and enzyme activities (Rossell et al., 2006), though not yet the time dependence of this regulation (see Table 1).

	Nitrogen starvation				Carbon starvation		
	ϱ_h	SEM	ϱ_m		ϱ_h	SEM	ϱ_m
GLT	1.2	0.1	-0.2		0.4	0.1	0.6
HK	1.0	0.2	0.0		0.1	0.0	0.9
PGI	0.8	0.3	0.2		0.0	0.0	1.0
PFK	0.4	0.2	0.6		0.4	0.4	0.6
ALD	1.1	0.5	-0.1		0.0	0.2	1.0
TPI	0.1	0.9	0.9		-0.4	0.2	1.4
GAPDH	0.7	0.5	0.3		0.1	0.0	0.9
PGK	0.0	0.2	1.0		-0.3	0.1	1.3
PGM	1.0	0.4	0.0		0.0	0.0	1.0
ENO	0.4	0.5	0.6		0.3	0.1	0.7
PK	1.4	0.3	-0.4		0.1	0.0	0.9
PDC	2.3	0.6	-1.3		0.1	0.0	0.9
ADH	1.7	0.4	-0.7		-1.3	0.2	2.3

Table 1 shows a preliminary steady state regulation analysis for carbon and nitrogen starvation performed in the Westerhoff laboratory. In the case of carbon starvation, regulation is largely metabolic for most enzymes, i.e., ϱ_h is close to 1 and ϱ_m is close to zero (note the exception for the glucose transport systems), whereas with nitrogen starvation we obtained a mixed picture of metabolic and hierarchical regulation (with quite an interesting role suggested for pyruvate decarboxylase). Pyruvate kinase (PK) and hexokinase (HK) should be excellent starting points for us; we should expect the ultimately dominant gene-expression regulation to be preceded by a much

quicker phase of metabolic regulation, as we know that a metabolic steady state is re-attained within a minute whereas the relaxation of gene expression to a new steady state takes hours.

Fig 1 shows that we have been able also to measure the corresponding mRNAs as a function of time using quantitative PCR. We have all the essential methodologies in place therefore. A nonessential methodology we do not yet have in place is the measurement of the protein concentrations of the glycolytic enzymes as a function of time after induction of nitrogen starvation. Setting up this methodology is part of the proposed work plan.

We also set the first steps for developing the theory behind time-dependent regulation analysis. We showed (unpublished) that the analysis inclusive of equations 1-2 above also applies to every point in time as well as to the difference between every point in time and the time before the regulation started to occur (we showed that this hinges on the occurrence of the enzyme concentration as a proportionality factor independent of all the other regulatory factors). We also derived an equation that is valid for the regulation for the rate of translation of mRNA of type i at every time point, where the last part of the equation defines the gene-expression regulation at the level of translation (ρ_{lti}) and the translation regulation (ρ_{ti}) itself, again quantitatively through the magnitudes of the corresponding coefficients. The latter coefficient may be further subdivided but we shall not focus on this issue in this research project. That equation shows that by (i) measuring the ratio of the mRNA concentration encoding pyruvate kinase between any time point during a regulatory phenomenon and the onset of that phenomenon and (ii) the ratio in protein synthetic rate of the enzyme pyruvate kinase between that time point and again the onset of the regulatory phenomenon, and (iii) by then dividing the logarithm of the result of (i) by the logarithm of the result of (ii), we shall obtain the gene-expression regulation coefficient for the regulation of the pyruvate kinase synthesis between time zero and time t. The translation-regulation coefficients will be calculated by subtracting ρ_{lti} from 1.

Experimental plan (6 subprojects)

1. Time-dependent experimental regulation analysis: metabolic versus gene-expression regulation (27 man months)

2. Time-dependent regulation in silico (9 man months)

3. Targeted quantitative proteomics (12 man months)

4. Regulation theory (6 man months)

5. Hierarchical time-dependent regulation analysis at the enzyme level (6 man months)

6. Hierarchical time-dependent regulation analysis at the translation level (12 man months)

Novelty, feasibility, risk analysis, justification

Novelty:

1. With functional genomics coming to fruition, systems biology has taken off. More and more of the networks in living cells are being characterized. In some cases, functioning of those networks is beginning to be understood, but the rate at which this understanding moves forward is limited. The limitation is no longer in the rate at which experimental data can be accumulated, but rather in the methodologies used to bring the data to bearing on regulatory mechanisms, and in the type of data that are collected. In regulatory mechanisms, the time factor is very important. This is certainly the case in systems biology, where feedback loops break linear causality (Westerhoff, 2005). We shall here develop a quantitative method for the analysis of the time-dependence of regulation. The method will reveal the sequence at which various regulatory mechanisms succeed or parallel each other.

2. At present it seems that almost separate communities analyze the transcriptome, the proteome, the metabolome, and the dynamics of macromolecules, respectively. Living cells are regulated through the involvement of all these four aspects, but not in a random way. The involvement of the four aspects is one of a democratic hierarchy where each factor directs other factors but is also directed by the same and yet other factors (Westerhoff, 2005). This

project will test our paradigm, and if we are right, will demonstrate experimentally at least one relevant example of biological, dynamic and hierarchical regulation.
3. The study builds on existing programmes in systems biology in Manchester, but extends the activity into both the analysis of hierarchical regulation and to the study of batch culture – a system much more representative of microbial growth in the wild and of the predominant mode of cell culture in industrial processes.
4. The method will also suggest types of experimental results and mathematical models that are particularly useful to obtain a deeper and more comprehensive understanding of how living organisms adapt to change.
5. Biology is subtle but, because of experimental limitations, many studies have not adequately reflected these subtleties. Our new method and the experimental methodology we will apply and refine, will help to set an example of how cell biology can become both more quantitative and more subtle.
6. The regulation analysis developed here differs essentially from, and adds to, metabolic and hierarchical control analysis (MCA, HCA). MCA/HCA establishes which molecular factors limit fluxes and concentrations. It does *not* analyze whether the cell makes actual use of those factors to regulate its behaviour, to adapt itself to changes in circumstances. Of course, MCA and regulation analysis together constitute a highly useful set of complementary methods to understand biological regulation in a way that overcomes previous conceptual and experimental limitations.

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PI's and their Track records

Hans V. Westerhoff has been active in what has become known as the field of Systems or Integrative Biology in the last 5 years. This stemmed from a longer history of study of phenomena in which the integrative actions of macromolecules produced effects that are essential for biological function, such as in free-energy transduction, DNA supercoiling, and yeast glycolysis. The effects are new or 'emergent' because the interactions are 'nonlinear' and this in turn implies that quantitative experimentation becomes important, as do more mathematical methods of analysis. Westerhoff has been promoting the implementation of this in combined experimental and theoretical research. In over 350 publications (http://www.bio.vu.nl/hwconf/papers/) including 11 citation classics (i.e. > 100 citations; the seminal experimental paper on Metabolic Control Analysis has 437), he and his research groups have developed various methods for quantitative analysis of biological systems, some of which are helpful starters for the newer fields of Systems Biology. These included a Mechanistic form of Non Equilibrium Thermodynamics, kinetic and stochastic methods for the analysis of metabolite channelling and non-equilibrium cooperativity, Hierarchical Control Analysis (a method extending the Metabolic Control Analysis of Kacser and Heinrich beyond metabolic pathways), and most recently Hierarchical Regulation Analysis, which is the subject of the present grant application. These developments were characterized by an integration of the theoretical aspects (including the derivation of mathematical theorems) with experimental results obtained in the Westerhoff laboratories.

In recent years, the research focus has been on the control, regulation and dynamics of yeast carbon and energy metabolism, on the control analysis of *E. coli* and mammalian signal transduction, on network-based drug design in *T. brucei*, on dynamic intermitochondrial communication in cardiomocytes, and on mitochondrial involvement in type-2 diabetes. The experimental systems and issues being diverse, the focus is on regulation and control of dynamic intracellular phenomena, much in the Systems Biology sense.

After staff positions at the (US) National Institutes of Health and the Netherlands Cancer Institute, Westerhoff became Professor of Microbial Physiology at the Free University Amsterdam and Professor of Mathematical Biochemistry at the University of Amsterdam. Recently, he also became the AstraZeneca-funded Professor of Systems Biology at the University of Manchester (60 %). Since much of cell biology requires synergistic input from many research groups and directions, he is setting up a European Centre for Systems Biology. Westerhoff is on various boards of Systems Biology programs (NSF-USA, Germany, Finland, BBSRC/EPSRC-UK) and has also been the main organizer of the first FEBS Advanced Course on Systems Biology (Gosau 2005) and one of the four organizers of the 2004 International Conference on Systems Biology (850 participants).

Douglas Kell has been active for more than 10 years in the application of advanced computational techniques to the explanatory analysis of complex (and heretofore mainly biological) systems. He founded the Aberystwyth Quantitative Biology and Analytical Biotechnology Group (http://qbab.aber.ac.uk), which pioneered the exploitation of spectroscopic and other strategies for the interrogation of minimally disturbed samples. He has published over 350 scientific papers (http://dbk.ch.umist.ac.uk/dbkPubs.htm), including 11 citation classics (plus 4 more papers with over 90 citations). He holds half-a-dozen patents, and serves on a variety of bodies including both the Council and the Strategy Board of the BBSRC and the NERC Environmental Genomics Committee. He has just finished a term on the RCUK Basic Technology Strategy Advisory Committee. He is a member of the EPSRC Peer Review College. He was Founding Director of Aber Instruments (http://www.aber-instruments.co.uk) which was set up to exploit his patented Biomass Monitor based on the use of non-invasive, radio-frequency dielectric spectroscopy. These instruments hold a world lead in this sector, and Aber Instruments received the Queen's Award for Export Achievement in 1998. He is also founding Director of a software house (Aber Genomic Computing, now Predictive Solutions Ltd http://www.predictivesolutions.co.uk/), set up to exploit Research Council-funded advances in machine learning. Since September 2002, Douglas Kell has held the EPSRC/RSC Research Chair in BioAnalytical Science in the Dept of Chemistry at UMIST http://dbk.ch.umist.ac.uk/, with a brief to continue to develop and exploit novel analytical methods for complex post-genomic biosystems, as per the present proposal. He has been awarded the 2004 Royal Society of Chemistry Interdisciplinary Science Award, the 2005 FEBS-IUBMB Theodor Bücher medal and a 2005 Royal Society/Wolfson Merit Award.

Stephen Oliver is Professor of Genomics in the Faculty of Life Sciences at Manchester. His research involves both experimental and bioinformatics approaches to functional genomics, mainly using the yeast *Saccharomyces cerevisiae* as his experimental system. Stephen Oliver led the European team that sequenced the first chromosome, from any organism, yeast chromosome III. He continued to play a major role in the Yeast Genome Sequencing Project, and went on to become Scientific Coordinator of EUROFAN, which pioneered a wide range of approaches to the systematic analysis of gene function, using *S. cerevisiae*. His current work aims at a complete understanding of the eukaryotic cell, using the yeast *Saccharomyces cerevisiae* as

a model system. Studies are being carried out on both the bioinformatic and experimental levels and exploit a range of comprehensive, high-throughput analytical techniques – transcriptomics, proteomics, metabolomics, and rapid phenotyping. Stephen Oliver is Coordinator of the BBSRC's Investigating Gene Function Consortium, COGEME (http://www.cogeme.man.ac.uk), and has direct responsibility for its Transcriptome Resource Facility. In this role, Prof. Oliver has gained considerable experience in the design, fabrication, and use of oligonucleotide-based microarrays. He is also deeply involved in the bioinformatic and statistical analysis of data from such arrays and from other 'omic technologies (see http://www.bioinf.man.ac.uk/microarray/maxd/ and http://www.cs.man.ac.uk/img/gims/;http://www.cs.man.ac.uk/~cornell/eFungi/eFungiFrontPage.html). Stephen Oliver is Chairman of the Wellcome Trust Molecules, Genes, and Cells Grants Committee and is Editor-in-Chief of *Yeast* and *Comparative & Functional Genomics*. He is a member of EMBO, a Fellow of the American Academy of Microbiology, and a Fellow of the Academy of Medical Sciences. Prof. Oliver was the Kathleen Barton-Wright Memorial Lecturer of the Institute of Biology & Society for General Microbiology in 1996, and won the AstraZeneca Award of the Biochemical Society in 2001.