COMBIO

Project no. LSHG-CT-2004-503568

Project acronym: COMBIO

An integrative approach to cellular signalling and control processes: Bringing computational biology to the bench

Instrument: STREP
Thematic Priority: Life Sciences

Publishable Final Activity Report

Period covered: from 01.03.2004 to 31.8.2007 Date of preparation: August 2007

Start date of project: 01.03.2004 Duration: 42 months

Project coordinator: Prof. Luis Serrano

Project coordinator organisation: CRG

Contract number: LSHG-CT-2004-503568

Title of the project: An integrative approach to cellular signalling and control processes: Bringing computational biology to the bench

Acronym of the project: Combio

Instrument type: STREP

Priority name: Life Sciences

Total project cost (in euros): 2,637,600.00

EU contribution (in euros): 1,998,000.00

Start date of the project: 01/03/04

Duration (in months): 42

Project web site: http://combio.crg.es

Project coordinator name: Prof. Luis Serrano

Project coordinator organization: CRG-Centre de Regulació Genòmica

Period covered: 01/03/04-28/02/07

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List of participants

Partic.Role*	No.	Participant name	Short name	Country	Date enter	Date exit
CO	1	Center for Genomic Regulation	CRG	Spain	Month 18	Month 42
CR	2	Centro Nacional de Biotecnologia	CSIC	Spain	Month 1	Month 26
CR	3	Weizmann Institute	Weizmann Institute	Israel	Month 1	Month 42
CR	4	Université Libre Bruxelles	ULB	Belgium	Month 1	Month 42
CR	5	Centro Nacional Investigaciones Oncologicas	CNIO	Spain	Month 1	Month 42
CR	6	UKG	UKG	Germany	Month 1	Month 42
CR	7	Budapest University of Technology and Economics	BUTE	Hungary	Month 1	Month 42
CR	8	BIOBASE GmbH	BIOBASE	Germany	Month 1	Month 42
CR	9	Parc Cientific de Barcelona	PCB	Spain	Month 7	Month 42
CR	10	European Molecular Biology Laboratory	EMBL	Germany	Month 1	Month 42

PROJECT EXECUTION

Project objectives

The major goal of COMBIO is to bring computer models and simulations to the experimental community. The focus has been on two key processes, which have been selected because they exemplify important and different biological systems. The first process is the p53-Mdm2 regulatory network, which can be approximated as a network of free components. The second system is the the spindle formation, the self-organization event whereby chromatin controls microtubule nucleation and organization and where localization, self-organization and gradient play fundamental roles. The added benefit of using these two systems is that they are already well characterized in the published literature.

COMBIO combines a unique team of experimentalists, bioinformatics and simulation groups, in order to gain a quantitative and dynamic understanding of these two key processes. A major objective is to benchmark the ability of current modelling and simulation methods to generate useful hypotheses for experimentalists and to provide new insights into biological processes of realistic complexity. The expected results are a set of guidelines, specifying which and how simulation methods should be used, given the problem at hand.

Work performed and results achieved

The project COMBIO started in March 2004 and it reached now its official end in August 2007. All partners within the consortium greatly contributed to the advance of the project and Deliverables and Milestones were fulfilled with only small adjustments due to unexpected advances in the field. 36 papers have been published in peer review journals and a few more are in press or in preparation. The research activities have been organized in five Workpackages: p53-Mdm2 network (WP1), mitotic spindle (WP2), database (WP3), visualization (WP4) and simulation strategies (WP5). The achievements within each WP will be highlighted in the following sessions.

Workpackage 1: Analysis of the p53-Mdm2 network

The transcription factor p53 is among the most studied proteins nowadays, considering that inactivation of the p53 pathway is a common, if not universal, feature in human cancers. The main objective of WP1 is to study the complex p53 network in a quantitative way, in various cellular contexts (i.e. mammalian or yeast cells) and under different conditions (i.e. normal conditions or stress-related conditions like drugs or irradiation). The groups developed novel sophisticated experimental strategies combined with profound computational analysis as well as system modelling. Work progressed in several directions.

In order to better grasp the regulation and dynamic properties of the p53 network, **Partner 1 (team 1)** created a novel synthetic p53 network in yeast. This experimental set up allows studying the system in living eukaryotic cells and at same time in “isolation”, since the yeast genome lacks the network ingredients. The team showed that Mdm2 is able to target p53 to degradation in unstressed yeast cells, to sumoylate p53 on the same residue modified in humans and then to localize p53-Mdm2 to nuclear bodies. This successful strategy sets the basis for investigating aspects of p53 regulation and dynamics and it could be applied in the future to study other complex networks in multi-cellular organisms.

Partner 3 developed a novel system to follow p53 and Mdm2 dynamics in individual living cells using a breast cancer cell line stably transfected with fluorescent labelled p53 and Mdm2 proteins. Time-lapsed fluorescence microscopy movies were recorded to study the dynamics of the transformed cells for extended period of times after exposure to different doses of gamma radiation. New mathematical approaches were employed in order to characterize the parameters of the p53-Mdm2 dynamics and describe the behaviour of the p53-Mdm2 negative feedback loop.

Partner 5 (team 1) generated a large number of “tools”, cell lines and vectors, to allow the COMBIO partners to study the p53 network. In addition, in order to identify new key players in the

p53 network, **Partner 5 (team 1)** used a systematic approach to select antisense RNA fragments able to inhibit the tumour suppressor function of p53. Different gene clusters were identified as new p53 regulators. Furthermore, in collaboration with **Partner 4 (team 2)**, gene array experiments were performed to analyse the variations of p53-dependent transcriptional activity in different cellular contexts. Different algorithms were applied to extract information from the arrays and to address questions such as: "which genes regulated by p53 are responsible of proliferating or arresting phenotype?" Additional studies were recently performed to study the effect of oncogenic ras in transcriptional activation induced by p53.

Finally, **Partner 3**, **4 (team 2)** and **7** devoted their efforts within WP1 to modelling strategies of the p53 network. **Partner 7** created a theoretical p53-Mdm2 model, based on the experimental data of **Partner 3** and including a positive feedback loop, in addition to the well known negative feedback loop. In addition, **Partner 7** further developed the model for the mammalian cell cycle, embedding the p53 dynamic in the cellular framework.

Overall, WP1 produced novel experimental tools (protocols, microscopes, cell lines, vectors) for a quantitative and dynamic analysis of the p53 circuit and provided new data to the modellers and simulators.

Workpackage 2: Microtubule self-organization: the mitotic spindle

WP2 focuses on the second biological system tackled by COMBIO: the self-organization process, whereby chromatin controls microtubule nucleation and organization during cell division. This network is not based on gene expression regulation but on different factors, such as localization, self-organizations and gradients. A combination of *in vivo* and *in vitro* studies has been used to study spindle assembly in the cell, alongside with theoretical modelling and simulations.

Partner 9 realized a visual database on spindle assembly. The database collects twenty seven time-lapse microscopy videos on spindle formation in different *Drosophila* live tissues: mature spermatocytes, syncitial embryos and larval neuroblasts (Figure 1).

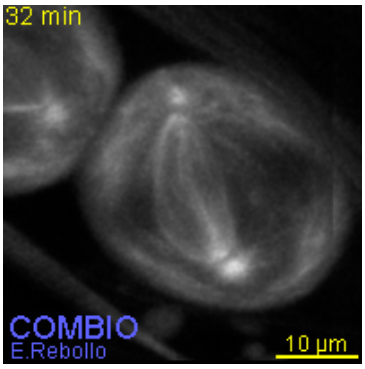

Figure 1 Frame of a spermatocyte movie showing the time and the scale.

This collection is now available to the scientific community through the COMBIO website (http://combio.crg.es/Videos/combio_video.html). By time-lapse microscopy, **Partner 9** focused more specifically in understanding non-centrosomal nucleation and the role of centrosomes in orienting the spindle during asymmetric stem cell division.

Partner 1 (team 2) worked on the characterization of the RanGTP regulated factors, such as TPX2 and Aurora A, using reconstitution experiments in a *Xenopus* egg extract system. Specific emphasis was given to the functional and structural characterization of TPX2 in *Xenopus*, humans and plants. Further experiments addressed the role of the kinase Aurora A (a well characterized TPX2 partner) localization and activation in the RanGTP dependent microtubule assembly pathway. By molecular modelling in collaboration with **Partner 1 (team 1)**, the TPX2-AuroraA interaction was extensively investigated.

In order to acquire more experimental data for further computer simulations of the mitotic spindle, **Partner 10** developed and implemented a microfluidic device to study the influence of chromatin on spindle morphology. The experimental set up consists of a chamber with groups of pillars. Plasmid DNA is attached to the top of the pillars and incubated with *Xenopus* egg extracts to induce spindle formation (Figure 2). This system allowed studying the influence of chromatin mass on microbulule nucleation and stabilization. The quantitative data collected was used for computer simulations with Cytosim, a software program developed by the group.

Concluding, WP2 paralleled the achievements obtained in WP1 by producing new experimental tools, new experimental funding and modelling exercises.

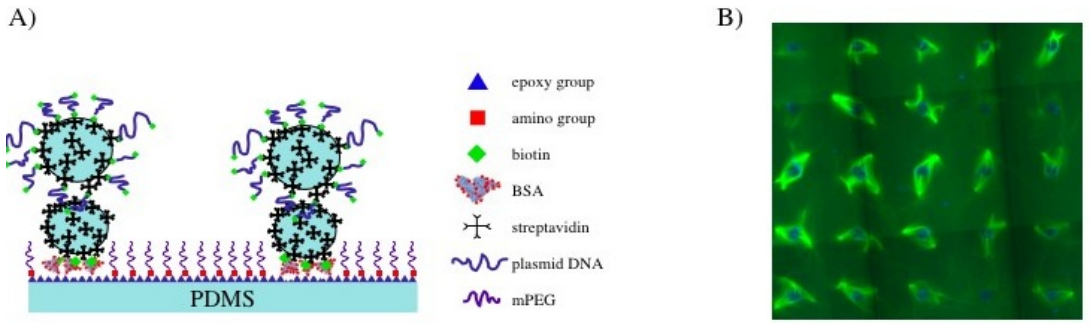

Figure 2 A) Scheme of the DNA patterning on a PDMS surface. B) Surface with patterns of DNA coated beads in blue and microtubules nucleated around them in green.

Workpackage 3: Database

The main objective of WP3 is to extend and complete the available information on the two networks under study, the p53-Mdm2 and the spindle system, with a focus on the network components, interactions and their orthologues. **Partner 5 (team 2)** created a common database where to store the available information on all the genes and proteins taking part in the two networks under study (p53 and spindle), including the knowledge acquired in WP1 and in WP2 as well as information from external sources. The database is available to the partners through the COMBIO website and will be soon released to the scientific community (Figure 3).

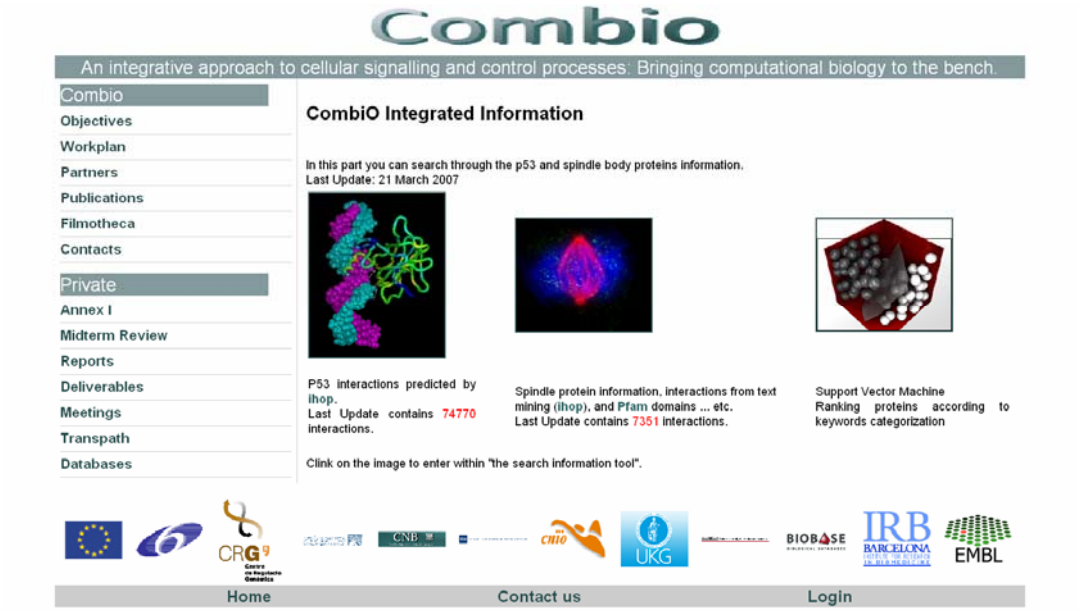

Figure 3 The COMBIO databases of interactions: p53 and Spindle. Additional information is available for spindle proteins using SVM technologies to categorize manuscripts mentioning the proteins.

In order to facilitate the analysis of protein sets by the experimental groups within COMBIO, **Partner 5 (team 2)** implemented the iHOP architecture (information Hyperlinked Over Proteins) to extract information from the literature and to annotate *in silico* the identified genes and proteins. Moreover, the team developed alternative approaches to "fish out" relevant information from bibliography. Text categorization tools were constructed based on Support Vector Machine (SVM) classifier strategies, for example to identify Spindle proteins relevant in the literature.

Partner 4 (team 1) and **Partner 8** coordinated their work in the annotation efforts of the two networks using the same repository. This database is TRANSPATH and focuses on signal transduction pathways in vertebrates. TRANSPATH is available to the partners of COMBIO through the project webpage. **Partner 8** collected information on reactions, molecules and protein interactions involved in the p53 and spindle formation networks. Figure 4 illustrates the Aurora B pathway as summarized in a clickable map, where mainly the pro-metaphase events around mitotic checkpoint are shown.

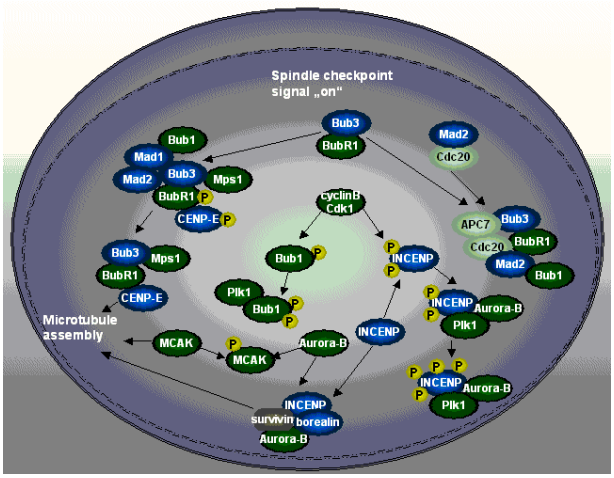

Figure 4 Map of the Aurora B pathway, as it is included in the TRANSPATH Professional since release 8.1 (March 31, 2007).

Partner 6 provided insights in modelling and representing the mammalian p53-Mdm2 network. Summing up, WP3 succeeded in providing to the consortium new tools to retrieve, annotate and store information on the p53 and spindle networks. A common database on the two biological systems was created and it will be soon released to the all scientific community.

Workpackage 4: Visualization

The main tasks of WP4 are to develop improved formal representations of signal transduction pathways as well as to develop tools for analysing and displaying the networks in a flexible fashion. Furthermore, since the partners involved in WP4 developed previously different database systems (TRANSPATH and aMAZE), it was also necessary to implement automatic protocols for loading and exchanging the data gathered in COMBIO from and between the databases and from the literature.

Partner 8 and **Partner 4 (team 1)** progressively improved the formal representations of signal transduction pathways and introduced these improvements in their respective databases, TRANSPATH and aMAZE. Moreover, both partners implemented their tools and environment for network visualization. Within TRANSPATH, as example, molecule highlighting, zooming and panning are now possible for any visualized network. **Partner 4 (team 1)** developed a workbench to allow smooth integration of multiple software for network analysis/visualization in the contest of aMAZE. Because of the importance of integrating all these new tools in a common environment, strong focus was given on automatic protocols for data exchange, mostly based on the BioPax

format, a community wide standard for pathway data exchange. Seamless traffic of data on interactions and pathways has been now enabled between the different biological databases.

Workpackage 5: Testing of different simulation strategies

By evaluating different modelling and simulation methods, WP5 aims to provide "guidelines" for defining the most appropriate modelling strategy for gathered experimental data, keeping in mind the process scale, the detail level and the features that the model should represent or any other addressed biological question.

First in the list of tasks, an interacting website was created to allow gathering and visualization of the models developed in the course of the project. Standards were also developed for information exchange between the teams. Secondly, to evaluate the different modelling methods, several distinct modelling approaches were applied by the partners to the p53-Mdm2 and spindle systems.

Regarding the p53-Mdm2 network, **Partner 1 (team 1)**, **Partner 3**, **Partner 4 (team 2)** and **Partner 7** used different qualitative and quantitative approaches and focused on different aspects of the response of the system to stress (such as digital oscillations, noisy oscillation amplitudes, variability in behaviour from cell to cell or in different cell types). The combination of these different techniques allowed revealing the richness of behaviour to be expected for the p53-Mdm2 network, and to reproduce and interpret several qualitative as well as quantitative features of the experimental observations for single cells and cell populations. **Partner 7** also investigated the need for using stochastic models to simulate the molecular changes during the cell cycle, a regulatory module closely linked to the p53-Mdm2 system.

Regarding the spindle system, modelling of spatial ordering was considered by **Partner 10**. The team largely extended their "Cytosim" program for simulating how microtubules and associated proteins, such as molecular motors, organize in space. Their simulation tool allows reconstituting and analyzing the formation of small anti-parallel-arrays of microtubules and is now being adapted in order to simulate larger assemblies such as those occurring in the mitotic spindle of human and *Xenopus* cells.

In line with the main final goal of COMBIO ("provide guidelines"), **Partner 1 (team 1)** published a review in *Nature* (Di Ventura *et al.*, Nature 2006: 443(7111):527-33) on main modelling and simulation methods, highlighting their respective limitations and advantages. The aim of the paper is to familiarize experimentalists with computational biology, which can provide additional tools to unravel the principles and operations of complex systems.

DISSEMINATION AND USE

Section 1 - Exploitable knowledge and its use

During the project COMBIO, the partners did not generate any results that are or will be exploited for industrial or commercial use.

Section 2 – Dissemination of knowledge

The dissemination activities below include those falling in the full duration of the COMBIO project.

Summary table

Actual Dates	Type	Type of audience	Countries addressed	Size of audience	Partner responsible /involved
Mar. 2004	Kick off meeting	Project partners	Europe	50	1, All
Nov. 2004	Workshop	Research	International	150	3
2004	COMBIO Website	Scientific community	International	n/a	1

2004	Conference	Research	International	500	4
2004	Conference	Research	France	n/a	4
2004	Conference	Research	International	200 - 450	7
2004	Summer school	Research	Europe	n/a	7
2004	Conference	Research	International	n/a	7
2004	Conference	Research	International	n/a	7
2004	Conference	Research	International	n/a	7
2004	Workshop	Research	International	n/a	7
2004	Publication	Research	International	n/a	1
Feb. 2005	1st AGM	Project partners	Europe	30	1, All
May 2005	WP meeting	Partners	Europe	10	4, 6, 8
2005	Conference	Research	International	500	1
2005	Workshop	Research	Europe	50	4
2005	Conference	Research	International	n/a	4
2005	Conference	Research	International	n/a	4
2005	BioPax meetings	Research	International	n/a	4
Dec. 2005	Conference	Research	International	200	6, 8
2005	Workshop	Research	Europe	n/a	4
2005	Advance Course	Research	Europe	n/a	4
2005	Workshop	Research	Europe	n/a	6, 8
2005	Workshop	Research	Europe	n/a	7
2005	Conference	Research	Europe	n/a	7
2005	EMBO Symposium	Research	Europe	n/a	7
Dec. 2005	Conference	Research	International	200	5
2005	Workshop	Research	Europe	n/a	4
2005	Conference	Research	Europe	n/a	4
2005	Conference	Research	International	n/a	3
2005	Publication	Research	International	n/a	1
2005	Publication	Research	International	n/a	4
2005	Publication	Research	International	n/a	7
2005	Publication	Research	International	n/a	7
2005	Book chapter	Research	International	n/a	7
2005	Publication	Research	International	n/a	9
2005	Publication	Research	International	n/a	9
2005	Publication	Research	International	n/a	8, 6
2006	Film/video on website	Research	International	n/a	3
2006	Conference	Research	Europe	200	1
Jan. 2006	Conference	Research	International	n/a	7
June 2006	Conference	Research	International	n/a	7
Nov. 2006	Conference	Research	International	n/a	7
March 2006	Conference	Research	International	n/a	7

Jun. 2006	Conference	Research	European	n/a	7
Oct. 2006	EMBO Workshop	Research	European	n/a	7
Feb. 2006	Lecture	Research	European	n/a	1
Apr. 2006	Conference	Research	International	n/a	1
Jun. 2006	EU meeting	Research	European	n/a	1
2006	Plenary Lecture	Research	International	n/a	1
Oct. 2006	Plenary Lecture	Research	International	n/a	1
Nov. 2006	Plenary Lecture	Research	International	n/a	1
Dec. 2006	Plenary Lecture	Research	International	n/a	1
2006	Conference	Research	International	n/a	10
2006	Conference	Research	International	n/a	10
2006	Conference	Research	European	n/a	4
2006	Workshop	Research	European	n/a	4
2006	Conference	Research	European	n/a	4
2006	Publication	Research	International	n/a	1
2006	Ph.D. Thesis	Research	International	n/a	1
2006	Publication	Research	International	n/a	1
2006	Publication	Research	International	n/a	7
2006	Publication	Research	International	n/a	7
2006	Publication	Research	International	n/a	3
2006	Publication	Research	International	n/a	1
2006	Publication	Research	International	n/a	1
2006	Publication	Research	International	n/a	1
2006	Publication	Research	International	n/a	1
2006	Publication	Research	International	n/a	9
2006	Publication	Research	International	n/a	6 & 8
2006	Publication	Research	International	n/a	6 & 8
2006	Publication	Research	International	n/a	6 & 8
2006	Publication	Research	International	n/a	6 & 8
Jan. 2007	New website	Scientific community	International	n/a	1
Mar. 2007	2nd AGM	Project partners	Europe	30	1, All
Feb. 2007	Conference	Research	Europe	n/a	4
Mar. 2007	Symposium	Research	International	n/a	9
Mar. 2007	Seminar	Research	International	n/a	9
May 2007	Seminar	Research	Europe	n/a	9
Jun. 2007	Conference	Research	Europe	n/a	9
Jan. 2007	Conference	Research	Europe	n/a	1
May 2007	Seminar	Research	Europe	n/a	1
Jul. 2007	Gordon Conference	Research	International	n/a	1
Aug. 2007	Seminar	Research	International	n/a	1
Aug. 2007	Conference	Research	International	n/a	1
2007	Publication	Research	International	n/a	9
2007	Publication	Research	International	n/a	6 & 8
2007	Publication	Research	International	n/a	6 & 8

2007	Publication	Research	International	n/a	10
2007	Publication	Research	International	n/a	7
2007	Publication	Research	International	n/a	7
2007	Publication	Research	International	n/a	9
2007	Publication	Research	International	n/a	9
2007	Publication	Research	International	n/a	10
2007	Publication	Research	International	n/a	10
2007	Publication	Research	International	n/a	4
2007	Publication	Research	International	n/a	4
2007	Publication	Research	International	n/a	7
2007	Publication	Research	International	n/a	4
2007	Book chapter	Research	International	n/a	7

Project meeting organized

Partner 1 (team 1) Kick off meeting held at EMBL Heidelberg, 02.03.04 and attended by representatives of all partners.

Partner 1 (team 1) AGM, EMBL, Heidelberg, 24.02.05 and attended by representatives of all partners.

Partners 4, 6 & 8 Working meeting of the TRANSPATH® team and aMAZE team 10.5.2005.

Partner 1 (team 1) "A cell in the computer", PRBB, Barcelona, Spain, 2006.

Partner 1 (team 1) AGM, CRG, Barcelona, 23.03.2007 and attended by representative of all partners.

Workshops & Conferences (Presentations and attendance)

2004

Partner 4 M. Kaufman, Colloque " Non-linéaire en Médecine et Biologie", France, 2004.

Partner 4 M. Kaufman, "Nonlinear dynamics and statistical mechanics days -Biological Applications", Belgium, 2004.

Partner 7 Novák B. & Tyson, J.J. (2004): Modelling the yeast cell cycle. *9th International Symposium on Computer Applications in Biotechnology.* Nancy, France, 28-31 March.

Partner 7 Novák B., Csikász-Nagy A., Kapuy O., Gyrffy B. & Tyson, J.J. (2004): Regulatory modules of cell cycle controls. *3rd International Fission Yeast Meeting.* San Diego, USA, 24 – 29 August.

Partner 7 Novák B. & Tyson, J.J. (2004): Modelling the yeast cell cycle. *2nd central European Conference – Chemistry towards Biology,* Seggau, Austria, 25 Sept - 1 Oct.

Partner 7 Novák B. & Tyson, J.J. (2004): Cell cycle modeling. *Symposium on Systems Biology,* Wageningen University, Netherland, 4 November.

Partner 3 U. Alon, 12th International p53 workshop, Nov. 2004

Partner 7 Novák B. & Tyson, J.J. (2004): Systems Biology of the Cell Cycle Engine. *Yeast Systems Biology, 2nd International Workshop.* Copenhagen, Denmark, 14-16 May.

Partner 7 Novák B. & Tyson, J.J. (2004): Dynamical modeling of regulatory networks. *Multiple Aspects of DNA and RNA: From biophysics to bioinformatics. Les Houches summer School,* Les Houches, France, 2-27 August.

2005

Partner 1 (team 1) L. Serrano, Keystone Symposium on Systems Biology, USA, 2005.

Partner 4 NCRR (Nacional Resource for Proteomics and Pathways) and the Open Source Comité of USHUPO. Workshop on Proteome Informatics. June 23-24. Ann Arbor, Michigan. USA.

Partner 4 ISMB 2005 Meeting of the internacional Society for Computacional Biology June 23

29. Detroit, USA. **Partner 4** Poster presentation "**aMAZE**: a multi-layer data model for biological processes" June 2005, ISMB.

Partner 4 Attendance at the two latest BioPAX meetings: in January 2005 (New-York, USA) and in June 2005 (Detroit, USA).

Partners 6 & 8 The 16th International Conference on Genome Informatics, Yokohama, Japan, December 19-21, 2005. Potapov, A.P., Voss, N., Sasse, N. and Wingender, E. Topology of mammalian transcription networks. *(submitted).*

Partner 4 M. Kaufman, W. Abou-Jaoudé, M. Traskine, Workshop "Dynamical modelling and analysis of biological regulatory networks", France, 2005.

Partner 4 M. Kaufman, Complexity Advanced Course "From functional genomics to molecular networks and back", France, 2005.

Partners 6 & 8 Potapov, A.P., Voss, N., Sasse, N., and Wingender, E. Emerging topological properties of mammalian regulatory networks. ESF Workshop on Transcription Networks: A Global View. 26.-28. May, 2005, Madrid, Spain. To be published in: *"ESF Workshop on Transcription Networks: A Global View. 26.-28. May 2005, Madrid, Spain"*, p.40.

Partner 7 Novák B. (2005): Modelling the mitotic and endoreplication cycles. *Plan Cell Cycle Workshop, Department of Plant Systems Biology,* Gent, Belgium, 15 March.

Partner 7 Novák B. (2005): Modelling cell cycle regulation in yeast. *Number to the models – generating data for Systems Biology, Goteborg, Sweden,* 10-12 June.

Partner 7 Novák B. (2005): The eukaryotic cell cycle: molecules, mechanisms and mathematical models. EMBO YIP Symposium on Quantitative Biology, Heidelberg, Germany, 2426 June.

Partner 5 (team 2) 16th International Conference on Genome Informatics (GIW 2005), December 19-21, 2005, Yokohama, Japan.

Partner 4 (team 2) Workshop "Computation of Biochemical Pathways and Genetic Networks", 12-13 September 2005, Heidelberg, Germany.

Partner 4 (team 2) IPG2005 Conference "Integrative post-Genomics: A multidisciplinary approach to living systems", 1-2 December 2005, Lyon, France.

Partner 3 FISEB Congress (Ilanit), Eilat, Israel, February 2005, International.

2006

Partner 7 Novák B. (2006): The Eukaryotic Cell Cycle: Molecules, Mechanisms, Modules and Mathematical Models. Abstraction, modularity and compositonality in gene and protein networks, Paris, France, 23-24 January.

Partner 7 Novák B. (2006): Mathematical models of the cell division cycle. Mathematics in the Brain: Computational models of cellular signaling in the nervous system. Kristineberg, Sweden, 7-13 June.

Partner 7 Novák B. (2006): Systems biology of the cell cycle. First Joint UK-Centres for Integrative Systems Biology Meeting, 27-28 November.

Partner 7 Novák, B. (2006). Exit from mitosis in budding yeast: models and experiments. *Genomes to Systems Conference 2006,* Manchester, UK, 22-24 March.

Partner 7 Novák, B., Queralt, E.& Uhlmann, F. (2006): Control of exit from mitosis. *Meeting of the Hungarian Bioinformatics Society,* Budapest, 12-13 June.

Partner 7 Novák B. (2006): Systems biology of chromosome condensation/decondensation. Systems biology meets chromatin function, EMBO workshop, Gossau, Austria, 12-15 October.

Partner 1 (team 1) Luis Serrano:24th February Seminar at the ETH, Zurich on Synthetic Biology

Partner 1 (team 1) 24th-25th April 2006, Meeting of the EU-USA task force on synthetic biology, Washington, USA

Partner 1 (team 1) June 30th 2006. Lecture on the COMBIO project at the EU meeting organized in Brussels on EC funded projects.

Partner 1 (team 1) 16th-18th October 2006. Plenary lecture at the Systems Biology Meeting organized in Wien, Austria by Giulio Superti-Fuga

Partner 1 (team 1) 2006. Plenary lecture at the Systems Biology meeting organized by Genopole in Paris.

Partner 1 (team 1) 30th November 2006. Plenary lecture at the Systems Biology symposium organized by the University of Lion.

Partner 1 (team 1) 10-11th December 2006. Plenary lecture at the Systems Biology Meeting organized by Marc Vidal at Namur, Belgium

Partner 10 Predictive models of complex systems, June 2006, Friday Harbor Laboratory, USA.

Partner 10 Workshop on Driven States in Soft and Biological Matter, Trieste, Italy, April 2006.

Partner 4 (team 2) Abstraction, modularity and compositonality in gene and protein networks, 23-24 January 2006, Paris, France.

Partner 4 (team 2) Workshop "Dynamics and structure of biological networks" - GeoCal06, 14-17 February, 2006, Marseille-Luminy, France.

Partner 4 (team 2) (C. Demol and M. Traskine) Third Bioinformatics Conference on Machine Learning for Microarray Studies of Disease, 15-16 September 2006, Genova, Italy.

2007

Partner 4 (team 2) Meeting “Dynamical systems methods in biology”, 1 February 2007, Ghent, Belgium.

Partner 9 Invited talk in the symposium "Stem cells and their chromosomes" 15-17/03/07, Kyoto, Japan.

Partner 9 Seminar in RIKEN Center for Developmental Biology, Kobe, Japan. 18/03/07.

Partner 9 Seminar at Institut Curie, Paris. 28/05/07

Partner 9 Invited talk at the “European Human Genetics Conference”. Nice, France. 17-19/06/07

Partner 1 (team 2) Invited talk at the ETH Biochemie, Zurich , Switzerland - January 25th,2007

Partner 1 (team 2) Seminar at the Cubimer, Sevilla, Spain, May 5th, 2007

Partner 1 (team 2) Invited talk at the Gordon Conference, Motile and contractile systems, Colby Sawyer College**,** New London, NH, USA**,** July 8-13, 2007

Partner 1 (team 2) Invited talk at the ´International Conference on Molecular Mechanism od Intracellular Transport: The Roles of Kinesin and Dynein Superfamily Proteins´ Tomakomai, Hokkaido, Japan August 23-26th, 2007

Partner 1 (team 2) Invited talk at the RIKEN Discovery Research Institute, Saitama, Japan August 28th, 2007

Publications

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Partner 1 (team 1) Di Ventura (2006) "Engineering a synthetic p53-Mdm2 network in budding yeast", Phd Thesis. Heidelberg.

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Partner 4 (team 2) Abou-Jaoudé W., Vikas F. and **Kaufman M.**, "Link between logical structure and dynamics: The example of the p53-mdm2 network" (in preparation).

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Section 3 - Publishable results

No industrially or commercially exploitable results were foreseen within the COMBIO project.