University of Pittsburgh School of Medicine
Department of Pathology
S701 Scaife Hall
3550 Terrace Str.
Pittsburgh, PA 15213

Zoltán N. Oltvai, M.D.
Tel: (412) 383-7408 Fax: (412) 383-9594 E-mail: oltvai@pitt.edu

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Prof. Yves Brun,
Systems Biology/Microbiology Faculty Search
Department of Biology, Indiana University
Jordan Hall 142, 1001 E 3rd St
Bloomington IN 47405-7005

Dear Dr. Brun,

It is a real pleasure to write on behalf of my former postdoctoral fellow, Dr. Gabor Balazsi, in support of his application for a faculty position at your Institution. I am a practicing Clinical Pathologist and an Associate Professor of Pathology at the University of Pittsburgh Medical School. My interdisciplinary research focuses on the organization of metabolic- and transcriptional-regulatory networks in model unicellular organisms, in collaboration with Prof. Laszlo Barabasi' group at the University of Notre Dame.

During his stay in my lab from January, 2002 through December, 2004, Dr. Balazsi's work has concentrated on two major directions. His own theoretical research focused on the understanding of information processing in living cells. Specifically, he focused on deciphering the principles of system-level function of transcription-regulatory networks, using microarray- and other experimental data. To this end, Gabor has first examined a key technical issue, i.e., how systematically collected microarray data is influenced by systematic bias inherent to the various experimental platforms? Using publicly available microarray data on synchronized *S. cerevisiae* cell cultures traversing through the cell cycle, he found that the printing of the probes on the microarray results in a major and consistent contribution to the observed gene expression levels that have a significant impact on the interpretation of gene expression measurements. He then reproduced the observed experimental bias by computer simulation and by a simple theoretical model. Based on this model, he developed a practical method to filter out the observed bias from measured microarray data (Balazsi et al, *Nucleic Acid Res.* 15, 4425-4433).

Next, Gabor focused on the issue of information transfer in the transcriptional-regulatory network of *E. coli*. Previous evidence indicated that potential regulatory interactions that together comprise the topology (i.e.,'wiring diagram') of transcriptional-regulatory networks are differentially utilized according to the environmental conditions in which a cell exists. Yet, the topological units underlying such differential utilization have remained undefined. Gabor reasoned that such utilization must be intimately intertwined with the mode of signal perception by the cell (Balazsi & Oltvai, *Sci. STKE* 2005, pe20). Specifically, he noted that -similar to the various sensory organs used for the human perception of smell, taste, light and sound-, cells use highly specialized 'sensor' proteins (and sometimes sensor RNAs) to detect concentration changes of nutrients, oxygen, variations of temperature, or the damaging effect of UV radiation. He then showed that due to the inherent directionality of information transfer the transcriptional-regulatory network of *E. coli* can be divided into layered hierarchies, which can be naturally decomposed to regulatory subnetworks that originate at a distinct class of sensor transcription factors. Using microarray data, he indeed found that specific environmental signals affect mRNA expression levels significantly only within the subnetworks responsible for their detection and processing. Finally, he demonstrated that small regulatory interaction patterns, called subgraphs and motifs, occupy distinct positions in- and among the subnetworks, and by generating a mass action kinetic model he provided insights into their dynamical role in information processing. I think that his work represents a seminal contribution to our understanding of the functional organization of transcriptional-regulatory networks, and will lead to a number of new and important questions regarding their system-level function. The paper summarizing these findings has been recently published (Balazsi et al, *Proc. Natl. Acad. Sci. U.S.A.,* 102, 7841-6).

Gabor's second interest in the lab was the bioinformatics analyses of data collected by his experimentalist colleagues, as demonstrated e.g., by a recent paper in the *Journal of Bacteriology* (185, 5673-5684), and one other currently in preparation, in which he has done most of the bioinformatics work. Gabor is very well suited to this, as he is a very nice, open-minded person who can confer at ease with his biologist colleagues and is quick to grasp the essence of various biological experiments. He is also an outstanding programmer.

In his own research he has the capacity to identify key original research problems, which then he doggedly pursues. I would also add that his participation at group meetings was just outstanding. His presentations of his own work are excellent, and I think he has the rare gift of the 'interdisciplinary teacher', who can easily explain difficult theoretical concepts to biologists, and biology to the theoretical physicists.

In conclusion, Dr. Balazsi is a hard working, highly productive, independently creative, outstanding young Biological Physicist. I support his application with utmost enthusiasm.

Sincerely yours,

Zoltan N. Oltvai