Modelling macromolecular networks: two meetings in Paris, July, 2002

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Two meetings were recently held in Paris and Evry under the auspices of the publically-funded research/biotech agency genopole® and of the Institut des Hautes Etudes Scientifiques. The first was a symposium, held July 8–11, 2002, which was devoted to "Macromolecular Networks", while the second was a workshop, which immediately followed the main meeting, July12–13, 2002, which was devoted to "Regulatory protein interplay and traffic on DNA". The Symposium focused on recent conceptual insights for identifying the dynamics of macromolecular interactions, the morphodynamics of biological structures and the nature of epigenetic processes. The Workshop concentrated on the control of macromolecular traffic on DNA and the interplay between regulating proteins acting on the same target gene. The sources of information for both were the rapidly growing amount of genomic, transcriptomic and proteomic data.

Addressing these issues requires interdisciplinary approaches, a fact reflected by the variety of scientific backgrounds of both speakers and audience.

In this report, we shall attempt to capture some of the spirit of these meetings, rather than trying to give a detailed summary of the findings; we apologize for any involuntary mis- or under-representations. Both meetings were co-organized with Paul Bourgine (CREA, CNRS/Ecole Polytechnique) and Misha Gromov (IHES).

Macromolecular networks come in three major flavours: metabolic networks, where interactions mostly involve enzymatic proteins and small molecules or metabolites protein–protein interaction networks and genetic networks, where regulatory proteins interact with promoter regions on DNA. These networks were analyzed in different talks from the physiological, comparative and informational angles.

The dominant view in biotechnology is that the phenotype/genotype relationship can be solved by appropriate population genetic-statistical treatments, especially in multigenic diseases. The first speaker, **David Weatherall** (Univ. of Oxford), however, began by giving us a salutary tour of well-studied monogenic diseases, thalassaemias, where this relationship still defies our full comprehension. Indeed, the findings show that even these so called monogenic diseases can behave as both polygenic conditions and environmentally triggered conditions. Evidently, even "simple" genetic diseases can show unwonted biological complexity. **John Tyson** (Virginia Polytechnic Inst.) followed this first talk and described a mathematical model of the cell cycle in fission yeast that integrates most factual observations in wild-type and mutant cells. Using dynamical systems, he analysed the cell cycle arrest points and transitions in terms of steady states and bifurcations, respectively.

Adam Arkin (Univ. of California at Berkeley) emphasized the interest of breaking down some of the regulatory networks into recognizable engineering functions, which can be done irrespective of the identities of their constituent genes. He described chemotaxis in neutrophil cells, where protein interactions are involved in sensing bacterial invaders and inducing actin contraction to target the movement of the cell towards bacteria. This example illustrated well a new level of complexity not previously seen in model chemotactic systems in bacteria. **Stanislas Leibler** (Rockefeller Univ.) discussed how spatio-temporal precision can be built by the working of genetic networks. His group's analysis of the morphogen gradients involved in the first steps of segmental patterning in *Drosophila* has revealed that, in early fly development, the noise in their positional information decreases between the first and second step of the transcriptional cascade. In effect, one property of complex transcriptional networks might be their general refinement (noise reduction) through successive rounds of operation.

Przemyslaw Prusinkiewicz (Univ. of Calgary) outlined the use of Lindenmayer-systems as a framework in modelling. He described recent progress on incorporating gene action into

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this framework, which was designed as a formal treatment of changing cell states in development. His approach allows the simulation of development in cyanobacterial filaments and in plant inflorescence, with the incorporation of known gene regulatory steps. **René Thomas** (Université Libre de Bruxelles) accorded an essential dimension to regulatory networks by comparing their logical and differential descriptions. He emphasized the importance of non-linear dynamics and the general role of feedback circuits in both ensuring stability and bifurcations in biological systems. **Michael Savageau** (University of Michigan) explained his theory of gene regulation in bacteria, which quantitatively relates the demand for gene expression in a natural environment to the molecular mechanism of gene regulation. He demonstrated the predictive capability of this demand theory in several cases. **Andreas Wagner** (University of New Mexico) tackled the question of how metabolic and protein interaction networks have been shaped. Does their present structure provide robustness against mutations ? He convincingly showed that theoretical models of network growth bear little relevance to the evolutionary processes that must lead to real-life networks. The question of network design was also addressed by **Uri Alon** (Weizmann Inst. of Sciences) in the case of transcriptional regulation (see below).

The next series of lectures focussed on information theory and its applications. **Henri Atlan** (Ecole des Hautes Etudes en Sciences Sociales) urged us to drop the naive exclusive focus on events at the genetic level. Drawing on examples in genomics and immunology, he presented an analysis of the behavior of a cell as that of a state machine. These concepts were examined further in a roundtable discussion. **Jacques Ricard** (Jacques Monod Institut, University of Paris) proposed that the equilibrium constant of an enzyme-catalyzed biochemical reaction be used as the probabilistic parameter in Shannon's (information theory) formalism. In this way, it becomes feasible to evaluate the information content of a metabolic network, which paradoxically can be higher than that of its parts, a case for formally defined ''emergence''.

Athel Cornish-Bowden (Marseille, CNRS) vividly pleaded for a systemic view of living organisms. He demonstrated how careful modelling of a metabolic pathway and analysis of enzyme inhibitor properties can guide the discovery of efficient drugs. Flux optimization in an unbranched metabolic pathway was the subject of the lecture by **Dominique de Vienne** (Univ. of Paris-Sud). Counterintuitively, he found that there are conflicting selective pressures between minimizing total enzyme concentration and coregulating enzyme production. **Philippe Marlière** (Evologic S.A.) appeared as a strong proponent of creating and observing artificial entities as a means to further our understanding of natural biology. He described advances in automated cultivation devices that allow rapid generation of new forms of bacterial life that may be customized for industrial bioconversion needs. The following round-table discussion allowed everyone to explore this exciting prospect.

Ambitious new technological approaches to various cell biological problems were also presented. **Hiroaki Kitano** (ERATO, Sony, Systems Biology Institute) presented new perspectives in the study and modeling of cell development, interaction and the spatial organization in multicellular organisms. He showed how cell division and fate could be automatically tracked in 3-D in the early stages of worm development, and how reproducible cell positions were from individual to individual. **Wolfgang Marwan** (Albert-Ludwigs-Univ.) elegantly demonstrated the use of time-resolved somatic complementation to systematically assign genes to the regulatory network governing sporulation in the slime mould *Physarum polycephalum*.

The peculiar properties of RecA, an enzyme that catalyzes the pairing of single-stranded DNA with complementary regions of double-stranded DNA, attracted a lot of discussions during both meetings. During the Symposium, **Albert Libchaber** (Rockefeller Univ.) described the nucleation/assembly and disassembly of RecA on single-stranded DNA. He expressed the controversial proposition that the assembly process can be regarded as a stochastic finite-state machine that conducts a basic computational operation, i.e. discriminate small differences between sequences of nucleotides. At the Workshop session on ''Traffic on DNA'', **Robijn Bruinsma** (University of California at Los Angeles) posed a number of stimulating questions about the topological and physical problems raised by the ability of a RecA–DNA complex to recognize the sequence of another DNA molecule. He proposed a statistical mechanics model of this recognition event and of the DNA strand exchange that follows it. **Marie Dutreix** (Curie Institut) discussed RecA-induced homologous DNA recombination as a paradigm for the search of a site on a long DNA molecule by a smaller molecule. The speed and efficiency of the reaction cannot be explained by Brownian motion or molecular tracking but presumably involves molecular translocations or inchworm local movements.

In the first talk at the Workshop, **Benno Müller-Hill** (Koln University), starting from the case of the lactose operon, mounted a strong case to support the idea that an increase in local concentration is a general and essential principle of the living matter, which in particular plays a great role in transcriptional regulation through DNA looping. **Andrew Lane** (University of Louisville) gave a detailed account of the energetics and dynamics of DNA-protein interactions, emphasizing the role of unstructured regions in the energetics of recognition.

The rest of the Workshop was devoted to ''Multigenic regulation.'' **Titus Brown** (CalTech) presented work done in Eric Davidson's laboratory on the regulatory gene network that underlies the endo-mesodermal specification during early development in the sea urchin. With 40 genes at hand, a formal

model that allows testable predictions was presented. In contrast with this case, where a single mutation in one of the genes suffices to produce a new phenotype, **John Reinitz** (State University of New York, Stony Brook) showed that the fly *eve* gene requires a combination of mutations on binding sites to observe a phenotype. He presented a refined three-tiered model of transcriptional regulation. Above direct DNA binding by factors, the second tier involves adapter molecules binding to DNA-bound factors, while the third tier includes a physical model of how adapters initiate transcription. The second tier is reminiscent of the approach presented by **Arndt Benecke** (Hŏpital Saint-Antoine and IHES) which involves exploiting for genome-wide identification of human DNA targets through identifing putative co-regulator sites.

Emmanuelle Roulet (University of Lausanne) described a bioinformatic-driven high-throughput method to define the sequence specificity of transcription factors, in the hope of identifying their binding sites and predicting their target expression. **Marcelle Kaufman** (Université Libre de Bruxelles) discussed the intricacies of the regulation of a gene that controls sex determination in flies. She presented a model that incorporates many biological observations and that can, in principle, serve to analyse a whole class of decision-making systems. **Uri Alon** presented an effort to delineate the design principles of transcriptional regulatory networks both through time-resolved gene expression monitoring in live bacterial cells and through a graph-theoretic approach to recognize basic building blocks in the whole network. He established some elegant relations between these basic blocks and their function in information processing. The last lecture was by **Cristoph Cremer** (University of Heidelberg) who introduced two new light microscopy approaches that allow unprecedented spatial resolution, potentially on live specimens. He beautifully showed how these methods, together with biocomputing methods, are starting to revolutionize our understanding of nuclear architecture and the relationships between chromosome organization and transcriptional status.

The workshop ended with general discussions on the value and future of delineating more systematically the frontiers of our understanding by means of modelling approaches in conjunction with new experimental technologies.