CONFERENCE REPORT

"EMERGENCE and EVOLUTION of DEVELOPMENTAL PATTERNS"

"*ORIGINE et EVOLUTION de SCHEMAS de DEVELOPPEMENT*"

Roscoff, France, April 25-29, 2012

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A first series of Jacques Monod Conferences centered on Developmental Biology took place between 1998 and 2003. The 2012 Conference on the *"EMERGENCE and EVOLUTION of DEVELOPMENTAL PATTERNS"* was the 1st of a new series aiming at bringing together established leaders in the fields of Cell, Developmental and Evolutionary Biology, in systems biology and mathematical modeling perspectives.

5 themes were addressed and combined at the conference:

- Tissue architecture, patterning and growth
- Gene regulatory networks
- Stem cells within tissues
- Developmental time
- Robustness and evolvability of biological patterns.

Program organization

In addition to 26 invited speakers, the program gave space to 18 selected presentations to allow for unforeseen discoveries to be presented. A vast majority of the selected presentations was given by recently established PIs, new promising leaders in their field.
7 invited speakers were from outside Europe, 9 from Europe outside France, and 10 from France.
3 selected speakers were from outside Europe, 8 from Europe outside France, and 7 from France.
The Female/Male ratio was 15/30.
Except for the keynote lecture (1h), plenary lectures were allocated 25 plus 5 minutes for discussion. Each short presentation selected from the submitted abstracts was ten plus 5 minutes. A dedicated chairperson was assigned to each session.
Each of the three poster sessions lasted 2.5 hours. In addition, the poster room remained accessible until 10 pm for additional presentations and discussions. The program also left ample opportunity for informal discussions amongst the participants both at lunch time and dinner/post-dinner time.

Scientific program

The first evening was dedicated to a keynote lecture by Eric Wieschaus, Nobel laureate (Physiology and Medecine 1995), *Princeton, USA*, who gave an illuminating view of cell shape movements that occur in a syncytial embryo when cell membranes cannot form. With his thought provoking presentation, the speaker highlighted the limitation of genetic analysis and stimulated a lively discussion about the need for new conceptual approaches to the problem of morphogenesis. This lecture was sponsored by *The Company of Biologists, UK*.

Tissue architecture, patterning and growth

The control of tissue architecture and morphological diversity in the animal kingdom was at the center of this session, which discussed cell signaling pathways and patterning events in various animal models.
Rudolf Winklbauer, *Toronto, Canada* used a combination of modeling and morphometric analysis to understand basic mechanical features of coherent tissue movement in Xenopus. **Kenji Matsuno**, *Osaka, Japan*, described how small asymmetric shape changes in every cell can account for the stereotypical looping of the Drosophila gut that characterizes left-right assymetry. During early development of the sea urchin, a signaling center in the ventral ectoderm sends morphogen signals, Nodal and BMP2/4 that control D/V patterning of the embryo. **Thierry Lepage,** *CNRS, Villefranche sur mer,* described a new mechanism controlling the range of Nodal signalling. Cnidarians, a sister group to bilaterians are of crucial importance to understand the evolutionary origin of Anterior-Posterior (A/P) axis patterning **Fabien Rentzsch,** *Bergen, Norway,* provided evidence that the development of the apical pole of cnidarians and the anterior pole of bilaterians are controlled by an ancient, plastic patterning module, supporting the hypothesis of homology between the aboral pole of *Cnidaria* and

the anterior pole of *Bilateria*. Notch-Delta signaling plays a critical role in generating distinct cell fates among groups of initially equivalent cells. From a quantitative time-lapse microscopy analysis of Notch-Delta signaling dynamics in individual mammalian cells, **David Sprinzak,** *Tel Aviv, Israel,* developed a mathematical model showing that the mutual inactivation of Notch and Delta proteins generates an ultrasensitive switch between sending and receiving signalling states. At the multicellular level, this switch facilitates the formation of sharp cell/tissue boundaries and provides insight into previously unexplained mutant behaviors. **Julie Ahringer,** *Cambridge, UK*, reported the results of genetic interaction RNAi screens for suppressors of *C. elegans* cell polarity mutants, connecting 184 genes, 80% having human homologs, and generating the most comprehensive metazoan polarity network to date. **Jeremy Reiter** *San Francisco, USA*, described the architecture of primary cilia, which act as critical sensors of extracellular information, and linked developmental defects in mouse mutant models to the Joubert and Meckel syndromes in humans. Some organs, such as segmented bony rays of the zebrafish caudal fin, can regenerate their correct shape and size following amputation. **Anne Gaelle Rolland-Lagan,** *Ottawa, Canada***,** reported a computational model which integrates the interaction of three morphogens and accounts for how the caudal fin acquires its normal shape and size following diverse types of amputations**.**

Despite substantial size variations, proportions of the developing body plan are maintained with a remarkable precision. It has been suspected that in Drosophila, individual organs inform the organism about their state of growth. **Maria Dominguez**, *Alicante*, *Spain* and **Pierre Leopold**, *INSERM*, *Nice*, identified a signal from growing organs that suppresses metamorphosis. Pierre Leopold also described his genetic analysis of how the brain responds to amino acid imbalance. Growth within an organ is also controlled by the process of cell competition, which promotes the elimination of weaker cells from a growing population. **Eduardo Moreno**, *Bern, Switzerland,* discussed evidence from his lab for an "extracellular code" that allows the weak cells to be recognized and eliminated. This code could constitute an ancient mechanism that resolves conflicts among competing cells thus ensuring harmonious organogenesis. **Jean-Paul Vincent**, *London*, *UK,* focused on the competitive nature of cells that over activate the Wnt pathway and discussed the contribution of JNK signaling to triggering apoptosis in such situations.

Gene regulatory networks

Elaborate gene expression patterns are a key feature of Development. Despite stochastic cell to cell variations, precision and robustness of gene expression is thought to be attained through a variety of mechanisms, including duplication of genes and/or gene transcription-regulatory elements, positive, negative and feed-forward regulatory loops, post-transcriptional regulation by miRNAs. These are some of the mechanisms that were discussed in this session.

Michael Levine, *Berkeley, USA,* described evidence for two distinct patterns of gene activation: synchronous, uniform and stochastic and proposed that transcriptional synchrony ensures the orderly deployment of the complex gene regulatory networks that control *Drosophila* embryogenesis. This lecture was sponsored *by The International Society of Developmental Biologists and Mechanisms of Development*. Many genes are controlled by multiple cis-regulatory enhancers. The precise DNA sequence of a particular enhancer changes over evolutionary time and this may or may not change its effects on gene expression. Michael Levine and **François Payre,** *CNRS, Toulouse,* reviewed recent insight into enhancer structure, communication between enhancers and how "shadow" enhancers foster robustness in gene expression in the face of genetic or environmental perturbations. **Scott Barolo**, *Chicago, USA,* discussed the special *cis*-regulatory logic of genes that respond to developmental signals that are deployed in many developmental occasions. Because cancer can arise from rare events happening in one or very few cells, it has been speculated that some genotypes could facilitate these events by increasing stochastic cell-to-cell variations (noise). **Gaël Yvert,** *CNRS, Lyon,* described how natural genetic variation influences the level of noise in yeast gene expression and the polygenic architecture of this “noise”. **Patrick Lemaire,** *CNRS, Montpellier,* linked cis-regulatory logics and the extent of divergence in transcriptional expression patterns that is compatible with morphological invariance across long evolutionary distances. **Albertha Walhout**, *Worcester, USA,* described a systems biology approach to the discovery of gene regulatory networks (GRNs) that orchestrate the spatiotemporal patterns of gene expression underlying nematode development. Autoregulation of sequence-specific TFs, which allows a tissue-specific memory effect, is a recurrent feature in development. **Pascale Gilardi-Henbenstreit***, ENS/CNRS/INSERM, Paris*, presented a

mathematical model of the *Krox20* autoregulatory loop which controls the patterning of the vertebrate hindbrain and the size of rhombomeres.

Stem cells within tissues

Resident stem cells in adult organs play an essential role in tissue homeostasis, regeneration and plasticity. The first potent Hematopoietic stem cells (HSCs) in mammals are generated in the aorta-gonad-mesonephros. **Elaine Dzierzak,** *Rotterdam, The Netherlands,* reported that HSCs arise directly from a subset of endothelial cells of the dorsal aorta in a natural transdifferentiation event and the role of the TF Gata2 which is upregulated during the hemogenic endothelial to hematopoietic cell transition. *Drosophila* definitive hematopoiesis takes place in a specialized organ, the lymph gland. A niche, termed PSC, is responsible for maintaining a pool of multipotent progenitors. **Alain Vincent**, *CNRS, Toulouse,* reported that controlling the size of the niche is essential for hemocyte homeostasis, drawing novel parallels between *Drosophila* and mammalian hematopoiesis.
All neural and glial cells of the vertebrate mature central nervous system derive from a limited pool of neural stem cells (NSCs). NSCs initially amplify through symmetric cell divisions, and then switch to an asymmetric mode of neurogenic division to produce their differentiating progeny. How this switch is controlled was highly debated during the Conference, based on live cell imaging in the developing chick neural tube. **Xavier Morin**, *CNRS, Paris,* reported that the mitotic spindle displays stereotypic movements during metaphase and that regulation of planar division is necessary to control proliferation in the neuroepithelium. **Kate Storey**, *Dundee, UK*, showed that divisions which separate apical and basal components generate an apical daughter cell which becomes a neuron and a basal daughter cell that rapidly re-establishes apico-basal polarity and divides again. These findings link division orientation to Notch signalling dynamics and the initiation of neuronal differentiation. NSCs reside in germinal zones (GZs) in the adult vertebrate brain. **Laure Bally-Cuif**, *CNRS, Gif sur Yvette*, described her genetic and live imaging approaches to identify molecular cascades and coordinated cellular behaviors which underlie NSC homeostasis in the GZ of the zebrafish adult telencephalon. She showed that Notch acts on NSC quiescence, correlating Notch signaling activity with cell division at the population level. In contrast to mammalians, adult zebrafish have a remarkable ability to regenerate adult brain. **Michael Brand**, *Dresden, Germany* reported that adult zebrafish can regenerate brain lesions from a subtype of ventricular radial glial stem/progenitor cells. Transcriptome analysis of progenitors isolated from lesioned adult brains identified novel genes that may function to control brain regeneration.

Developmental time

In addition to spatial cues, temporal patterning cues regulate many different developmental decisions.
During nervous system development, neural progenitors divide to generate a multitude of neural sub-types. **Stefan Thor**, *Linköping, Sweden,* presented recent progress in understanding how temporal competence changes intersect with lineage tree shape and lineage size, to control the proper numbers of each neuron type in the Drosophila CNS. The medulla of the *Drosophila* visual processing center, the optic lobe, contains 40,000 neurons, which belong to more than 70 cell types, and are born sequentially from NSCs. **Claude Desplan,** *New York, USA,* showed that during medulla development, neuroblasts sequentially express five TFs in a temporal manner, and that the neurons generated in this sequence become different cell types at stereotypic positions. The zebrafish pineal gland contains two main cell types: Projection Neurons (PNS) and Photoreceptors (PhRs) of three distinct subtypes. **Elise Cau**, *CNRS, Toulouse,* reported that that PhRs can be born from two different types of divisions and that timing plays a critical role in the specification of the subtypes.
In the vertebrate neural tube, Sonic Hedgehog (Shh) acts as a morphogen to control the pattern of neuronal subtype specification. A spatially and temporally changing gradient of Shh signaling is interpreted by the regulatory logic of a downstream transcriptional network. **James Briscoe**, *London, UK,* presented a mathematical model of this network. Its design renders cells insensitive to fluctuations in signaling and confers hysteresis--memory of the signal; morphogen interpretation thus provides robustness and reliability to tissue patterning. In *Drosophila*, the Bicoid morphogen is itself a TF. **Nathalie Dostatni**, *INSERM/Institut Curie, Paris*, measured the mobility of Bicoid molecules using fluorescent correlation spectroscopy (FCS). Fast mobility reconciles the physical limits of the simple diffusion system with the rapid robustness of the response to the Bicoid gradient. A population of genetically oscillating cells termed the segmentation clock is hypothesized to control the rhythmic and sequential formation of vertebrate body segments. **Andrew Oates**, *Dresden, Germany,* reported the

identification of the first segmentation clock period mutant. Multiple-embryo time-lapse microscopy of zebrafish embryos revealed that the period of the segmentation clock is regulated both at the single-cell level and by intercellular signaling.

Evolvability and robustness of biological patterns

Biological systems display the inherent property of robustness to intrinsic or environmental fluctuations. Developmental plasticity is a key adaptive process allowing organisms to cope with changes in their environment by modulating the phenotypes produced by a given genotype.
How plants cope with both plasticity and robustness was discussed by **Alexis Maizel,** *Heidelberg, Germany,* based on development of the *Arabidopsis thaliana* root system. He presented recent advances on the morphodynamics of lateral root formation, in particular the role played by physical constraints. **Kirsten Ten Tusscher,** *Utrecht, The Netherlands,* reported computer simulations to investigate the evolution of body plan patterns that are both segmented (metamerism) and differentiated (Hox-like pattern). Simulations suggest that evolvability may arise as a side effect of selection for robustness. In turn, selection for robustness might explain why the vertebrate-type clock- and wavefront mechanism became the dominant evolutionary outcome. Prominent model organisms, such as *Drosophila*, *C.elegans* or the mouse, allow to survey only a small fraction of the morphological and functional diversity present in the animal kingdom. **Michalis Averof,** *Heraklio, Crete, Greece,* described developmental genetics tools in the beetle *Tribolium castaneum* and the crustacean *Parhyale hawaiensis*. His most recent work provided evidence for a segmentation clock in these species, as in vertebrates. Is genetic evolution predictable? **Virginie Orgogozo,** *CNRS, Paris*, reported an interesting case: the dependence of *Drosophila pachea* on its single host, the cactus Lophocereus schottii, because *D. pachea* lost the capacity to transform cholesterol into 7-dehydrocholesterol. She linked this loss to four amino acid changes in the Neverland protein, illustrating how a few genetic changes in a single gene may restrict the ecological niche of a species.
Sexual conflict is thought to be a potent force driving the evolution of sexually dimorphic traits. **Abderrahman Khila,** *CNRS/ENS, Lyon,* described a set of sexually dimorphic traits and their role in the conflict over mating rate between males and females of the water strider *Rheumatobates rileyi.* He then showed *a* role of the *distal-less* gene in the evolution of these traits, connecting changes in animal morphology, their underlying genetic basis, and the associated fitness advantage.
One key question regarding phenotypic evolution is the respective role of random genetic variation and natural selection. Nematode vulva development provides a model system to study this question. The relative evolvability (mutational variance) of different vulval cell fate variants was measured by **Mary-Anne Félix** *CNRS/ENS, Paris*, in random mutation accumulation lines (lecture sponsored by *Société Française de Biologie du Développement*). She could conclude that mutational effects may produce phenotypic trends, in the absence of selection.

General comments

The total number of participants to the Conference was 108. It included 57 Principal Investigators, 34 post-docs and Research Associates and 17 PhD students. Selected applicants originated from 11 different European Countries, Australia, Canada, India, Israel, and USA.
The overall quality of the talks was outstanding, and the numerous questions raised after each talk lead to stimulating, lively discussions. All 5 oral sessions and 3 poster sessions were very well attended. The choice of Roscoff for organizing this first conference of a new series was particularly appropriate since it fostered informal, yet rigorous scientific exchanges.
The success of the conference could be judged from the request by many participants for another meeting in 3 years and from numerous “thank you’ emails that we received after exchanges. We also want to highlight the helpfulness of the Roscoff CNRS staff members, the quality of the meals, and the tireless work of Dominique Lidoreau, before during and after the Conference. The success of the conference could be judged from the request by many participants for another meeting in 3 years and from numerous “thank you’ emails that we received after the conference.
The growing momentum of systems biology provides a strong impetus to organize this conference on a regular basis, alternating with the Developmental Biology Gordon Conference organized in New Hampshire, USA, every 3 years. Jean Paul Vincent, vice-chair accepted to chair the next conference in the series, and Laure Bally-Cuif, CNRS, Gif sur Yvette was co-opted as the next vice-chair.