

Commemorative Symposium for the 27th International Prize for Biology
Special Lecture
(Thursday, December 1, 2011, 4:30pm-5:45pm; Kyoto Garden Palace, Aoi room)

Genomic control logic of development

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Pregastrular specification in the sea urchin embryo consists of establishment of specific territorial regulatory states during cleavage and gastrulation, where regulatory state denotes the sum total of specifically expressed mRNAs encoding transcription factors. The initial asymmetric inputs into the specification system are maternally localized anisotropies of regulatory significance, and thereafter the spatial diversification of regulatory states depends on genomically programmed intercellular signaling. By gastrulation the whole embryo is a mosaic of regulatory states which foreshadow and causally control the post-gastrular development of the parts of the embryo. The developmental specification process occurs the same way in every embryo of the species, differently in different species, and is hardwired in genomic control sequences. To achieve a system wide causal explanation of the developmental process, a DNA level solution of the genomic control program is required. This program is comprised of the *cis*-regulatory modules which determine the activation and repression of regulatory genes, specifying their inputs, their logic processing functions, their interactions and their targets, and secondarily thereby controlling the mobilization and interpretation of signal systems. The gene regulatory network (GRN) generated by operation of the pre-gastrular control program has been solved for about half the sea urchin embryo up to gastrulation, that half producing the skeletogenic mesoderm, the oral and aboral non-skeletogenic mesoderm, and the anterior and posterior endoderm (GRNs for the remainder of the embryo will soon also be available). The endomesoderm GRN contains >60 mainly regulatory genes. Its structure alters dynamically during development, as given genes are turned on and off in given spatial domains. The GRN was solved over the last decade by a combination of high resolution spatial and temporal observations on gene expression, very large scale perturbation analyses in which the effects of blocking expression of each gene on other genes were measured, and extensive experimental *cis*-regulatory studies. If the GRN indeed completely represents the genomic control program, it should contain sufficient information to enable predictive generation *in silico* of the dynamic progression of spatial regulatory states. To test this we have built a dynamic Boolean model of pregastrular sea urchin endomesoderm development, using the information in the GRN structure at each node to generate logic equations that specify the regulatory behavior of each gene. The dynamics were assumed from a previous first principles kinetic analysis. The model behaves as an automaton, and in fact successfully re-creates the observed regulatory gene expression patterns with perfect spatial fidelity and near perfect temporal fidelity. Those points at which knowledge is yet insufficient are immediately illuminated, but the overall conclusion is that this model demonstrates our experimental GRN analysis to be approaching completion; more generally it proves that the requisite information for the embryonic specification process is indeed located in the genomic regulatory code. The model was also used for *in silico* perturbations of gene expression and regulatory exploration of embryological experiments. The observed results of these experiments were regenerated in regulatory state terms by the automaton model, including additional predictions. In sum, this research shows how the genomic regulatory system controls embryological development.