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Modeling, simulation and analysis of *C. elegans* development

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Various fields of biology will soon progress to a complete cataloguing of the basic molecules and cells comprising their systems of interest. Biology in the 21st century will direct its attention towards understanding how component parts collaborate to create a whole system or organism. The transition from identifying building blocks (*analysis*) to integrating the parts into a whole (*synthesis*) will have to use the language of mathematics and algorithmics. We need a language that is legible both to biologists and computers, and that is faithful to the logic of the biological system of intrest.

In search for an appropriate rigorous approach to modeling biological systems, we examined formal modeling methods in computer science that were originally developed for *system design*. In two recent publications, we described our use of the *visual formalism* of statecharts to address the challenge of synthesis. We presented a detailed model for T cell activation using *statecharts* within the general framework of object-oriented modeling (Fig. 1). We have recently initiated a far more ambitious project, applying the same methodology for constructing a fully detailed model of the developmental processes that lead to the formation of the egg laying system in *C. elegans.*

The egg laying system in *C. elegans* consists of four compartments: (i) the gonad, (ii) the vulva, (iii) uterine and vulval musculature and (iv) the bilaterally symmetric HSN neurons.
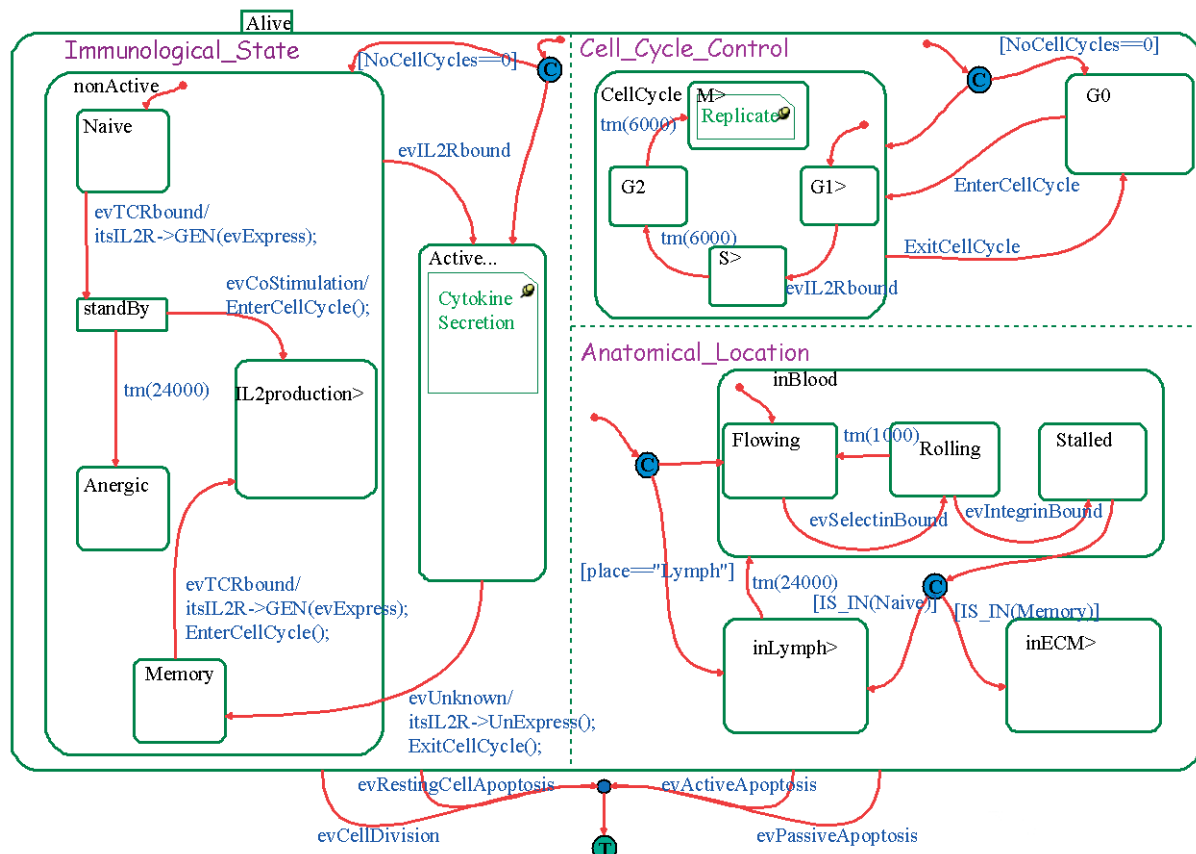

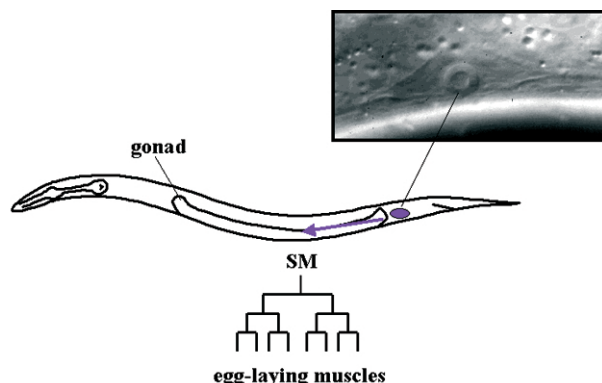**Fig. 1** *Statechart of a T-helper Cell object class.*

Fig. 2 *The Sex Myoblasts (SMs) migrate anteriorly to generate the egg-laying muscles in functional positions.*

Proper functioning of all four components of the egg laying system is required for egg laying to occur. Cell interactions play a major role in animal development. The developmental events coordinate the formation of the egg laying system formation in *C. elegans* involve both interactions that occur among cells within the same tissue (e.g., the lateral signaling between the vulva precursor cells) and interactions between cells in the different participating tissues/organs (e.g., signals from the gonad that govern the migrations of the sex myoblasts (Fig. 2), signals produced by the gonad that affect cell fate determination in the vulval precursor cells). Modeling such phenomena introduces various challenges, such as organizing a large number of biological objects in a hierarchical fashion and relating various cellular events within the spatial and temporal context in which they occur. In addition, modeling the development of the egg laying system in *C. elegans* relates to the more general challenge presented above: understanding how component parts in a nontrivial biological system collaborate to create a whole.

In our previous modeling of T cell activation, we showed the applicability of a statecharts-based approach to cope with these and other challenges. In the current work we apply the same modeling approach to developmental processes in *C. elegans*. Such models are useful for investigating the behavior of the system under many given scenarios, raising questions that were not thought of before and confront questions, which, because of their complexity, cannot be addressed by standard laboratory techniques and/or pure intuition alone. In addition, we plan to use *formal verification* methods in order to test whether the formal representation of the model fulfills the requirements that emerge from existing biological data, and to discover unexpected behaviors both of the model and of the biological system. Finally, in this modeling project we aim at constructing a fruitful interaction between computational modeling and experimental lab work.

Selected Publications

Kam, N., Cohen, I.R., Harel, D., and Pnueli, A. T cell activation: Statecharts-based modeling and verification. Technical report, The Weizmann Institute of Science, Rehovot, Israel. (in press).

Kam, N., Cohen, I.R., and Harel, D. The Immune System as a Reactive System: Modeling T Cell Activation with Statecharts. Bull. Math. Biol. (in press). An extended abstract of this paper appeared in Proc. IEEE Symposia on Human-Centric Computing, IEEE Computer Society Press, September 2001, 15-22.

Kam, N., Harel, D., and Cohen I.R. (2001) Modeling Biological Reactivity: Statecharts vs. Boolean Logic, Proc. International conference on Systems Biology, Pasadena, CA, USA.

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