Cooking up a recipe for simulations: COMBIO project to set guidelines for systems modeling

It's all the rage today to simulate biological systems in the computer New methods are revealing how complex biological processes really are, and understanding them will require models. But what programs can handle the task, and to what level of detail should a model go? Luis Serrano doesn't have a definitive answer, but he's mapped out a strategy to find one, drawing on a solid history of model-building at EMBL. His plan was so good that it was awarded an EU integrated projects grant totalling nearly 2 million euros. The project is called COMBIO, and it involves nine partners from across Europe. Their goal is to come up with a set of guidelines for how to help scientists in the lab use mathematical tools to understand biological systems.

There are many factors that can influence how a biological process takes place (for example, the type, number and concentration of molecules that need to be present, where in the cells things happen, and the element of randomness). Models and simulations try to recreate the different scenarios and predict what will happen when one or more of the factors changes. But how do you tell the difference between a good computer modeling system and a bad one? And how do you know whether or how you can apply it to your project?

"You don't," says Luis, "at least not yet. There are no clear guidelines on which tools are best to use. We're not even sure which level of detail is needed to understand a biological system. Our idea was to combine experts working on different aspects of systems biology problems come up with a recipe book."

Luis and his colleagues (including François Nédélec, Isabelle Vernos and EMBL alumna Shoshana Wodak) will use two different model systems: p53-MDM2, a gene network involved in programmed cell death; and the process of chromatin-controlled microtubule nucleation and organization. The groups in the consortium have a lot of experience working with these systems, so testing them will be easy.

"The p53-MDM2 system is interesting because it has an oscillating cycle," says Luis. "It has been proposed that different genes may get transcribed as the frequency of the cycle varies and this could determine whether or not the cell dies through apoptosis. Spatial factors are also an important aspect of this system – one that we are particularly interested in. Proteins come in and out of the nucleus and this may be important for the activity of the cell. The idea is to understand the role of stochasticity, space and delays on the simulation of the p53/MDM2 network."

The other model is the mitotic spindle, an area of research that Isabelle and François and other EMBL groups have worked on for many years. It provides a good well-known experimental system *in vitro* that is controllable.

Experimental groups will be working on the cell biology of the two systems. Bioinformatics groups will support them with information on missing genes, for example, or by providing information on networks in which the genes are known to be involved. Then they'll pass their results to the simulation groups, who will recreate the different scenarios on their computers, with the ultimate goal of drawing generic conclusions for the guidelines.

Luis and colleagues will make the guidelines, along with the models and software produced along the way, available to the research community via the project website. In the meantime, the COMBIO consortium will have their first annual meeting at EMBL-Heidelberg on February 24 to take stock of the progress on the cookbook.

www.pdg.cnb.uam.es/COMBIO/

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All roads lead to Milan and Monterotondo: ELLS goes to Italy

In 2004, ELLS travelled south to forge sustainable links between teachers and research institutions in Italy. Our first port of call was Milan.

The idea of organizing a course in Milan started to germinate about one year ago, when Maria Luisa Technini, an EMBL alumna who is a Genetics Professor in Milan Medical School, contacted ELLS. Together with the *Ufficio Scolastico de la Lombardia*, Maria Luisa had already established the CUS-Bio (Centro Università-Scuola per le Bioscienze) bringing together scientists, teachers and students in Milan University. A very successful course "*Ingegneria genetica e sue applicazioni*" for a group of 150 teachers had already taken place in the spring and Maria Luisa was hoping to organize another course in collaboration with ELLS for the autumn. As part of the collaboration, Silvia Boi, a postdoc-turned-teacher, who is now a full-time member of CUS-Bio, spent June at EMBL adapting ELLS' activities to their needs. CUS-Bio also hired a second full-time member, Cinzia Gracioli, an experienced science teacher particularly skilled in audiovisual technologies applied to teaching.

For three afternoons, 30 Italian teachers participated in the first ELLS-CUS-Bio LearningLAB, "From Organisms to Genes," following the development of fish embryos, performing fish mutant genotyping by PCR and hunting a protein on the web in a bioinformatics activity. ELLS Education Officer Alexandra Manaia flew in from Heidelberg to lend a hand in the wet labs, and EMBL Computer Scientist Francesca Diella led the bioinformatics activity. But most of the work was carried out by the local team who did a wonderful job: the CUS-Bio staff Silvia and Cinzia, Professors Maria Luisa Technini, Paolo Plevani, Giovanna Viale and Franco Cotelli, and Milan University fish experts. CUS-Bio has got off to strong start with a full schedule of exciting activities for the future, including an e-learning module based on the course "From Organisms to Genes" developed in collaboration with ELLS (see http://users.unimi.it/cusbio.)

ELLS' second port of call was EMBL's Monterotondo Outstation, for a LearningLAB on "Stem Cells: promises and challenges." Cornelius Gross, who did a brilliant job coordinating the Monterotondo scientists, gave a general overview of the course. Fresh off a flight from Singapore, Nadia Rosenthal, the Outstation Director, gave an outstanding talk on stem cells and their applications. Following protocols carefully selected and adapted by Walter Witke, young EMBL scientists Rossana De Lorenzi, Daniela Ruffell, Carla Sciarretta and Arianna Nenci guided the teachers through exciting hands-on activities. José González and his collaborators demonstrated blastocyst microinjection.

For the closing act, ELLS were very fortunate to benefit from the collaboration of two Branco-Weiss Science-in-Society Fellows: Giuseppe Testa and Giovanni Frazzetto. Giuseppe gave a great talk on bioethical implications of stem cell technologies, followed by a lively role-play game designed by Giovanni. The teachers also had fun playing "The Stem Cell Game," a board game developed by ELLS.

The Monterotondo team did such a great job and the teachers' response was so positive that we are all already dreaming of the next Monterotondo LearningLAB!

– The ELLS team

Photo by Immacolata Ercolino.

Italian science teachers at the bench.