UNIVERSITÀ DEGLI STUDI DI PERUGIA
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Il giorno **giovedì 24 settembre, alle ore 16**, presso l'**aula magna** della Facoltà di Ingegneria, Università degli Studi di Perugia, si terranno due seminari di *Systems Biology* a cura del Dipartimento d'Ingegneria Elettronica e dell'Informazione.
Il tema, interdisciplinare, è di grande attualità. Tutti gli interessati sono invitati a partecipare. I due seminari sono di particolare interesse per gli studenti di dottorato.

Il primo seminario, dal titolo

Modeling of the stochastic white-opaque switch in *Candida albicans*

sarà tenuto da **Cihan Oguz**, attualmente presso University of California San Francisco, Department of Biochemistry and Biophysics,El Samad Systems Biology Lab.

Il secondo seminario, dal titolo

Parameter Estimation and Model Selection in Computational Biology

sarà tenuto da **Gabriele Lillacci**, che collabora con il Center for Control, Dynamical Systems and Computation, University of California, Santa Barbara.

Di seguito un breve abstract dei due interventi

Prof. Paolo Valigi

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Modeling of the stochastic white-opaque switch in *Candida albicans*

Cihan Oguz
University of California San Francisco, Department of Biochemistry and Biophysics.
El Samad Systems Biology Lab

The human fungal pathogen *Candida albicans* is the cause of serious invasive diseases in immunocompromised patients. *C. albicans* has the ability to stochastically switch between distinct white and opaque cell types that seem to have different pathogenic potentials. Although the switch from white to opaque is accompanied by a change in the transcriptional profile of hundreds of genes, recent experimental investigations identified four major transcriptional regulators (Wor1, Czf1, Efg1 and Wor2) responsible for implementing the switching decision. A deterministic model that uses ordinary differential equations and mass action kinetics is used to describe the gene regulatory network that implements the white-opaque switch. This model is appropriate to describe the behavior of the system upon ectopic overexpression of some of the regulators (such as Wor1 and Czf1) where deterministic mass conversion to the opaque phase occurs. It can also accurately describe the bistable nature of the WT system without the overexpression of the regulators. Experimental data from the literature [1] was converted to inequality constraints between the protein levels at steady state, and used in combination with Latin Hypercube sampling of the parameter space of the deterministic model to constrain parameter ranges in the WT system (e.g. activation/repression coefficients, protein degradation rates). To further refine the biochemical parameters, this initial coarse tuning of the parameters was followed by a fine tuning step. Starting with the sets of parameters that satisfy the experimental inequality constraints between the protein levels, a global optimization technique based on differential evolution, was used to refine model parameters by minimizing the difference between experimental data (ratios of protein levels under different conditions) and model predictions/. /The deterministic model with the parameter sets obtained from differential evolution was then converted into a stochastic model, which was probed using stochastic chemical kinetics and Monte Carlo simulation. This stochastic model was able to reproduce some experimentally observed trends such as the significant impact of Wor1 and Czf1 copy numbers on the white-to-opaque switching frequency, the insensitivity of this frequency to the number of copies of Wor2, and the increased stability of the opaque state with higher number of Wor1 copies compared to WT . The model also generated many important predictions. For example, we predicted that for all basal transcription rates, that of Czf1 would have the largest effect on white-to-opaque switching frequency. We also predicted that white-to-opaque switching frequency would increase significantly with Efg1 degradation rate and that stability of the opaque state would be very sensitive to the Wor1 degradation rate. Future work in this study involves refining the model to account for some inconsistent experimental data in order to assess the functions of the components and the feedback loops in terms of their effects on the switching frequency and the heritability of white and opaque states.

[1] Zordan R.E., Miller M.G., Galgoczy D.J., Tuch B.B., Johnson A.D. (2007) Interlocking transcriptional feedback loops control white-opaque switching in Candida Albicans. PLoS Biology 5:2166-2176.

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Parameter Estimation and Model Selection in Computational Biology.

Gabriele Lillacci

Abstract: Parameter estimation is a key issue in computational and systems biology, as it represents the crucial step to obtaining quantitative, or even qualitative, information from dynamical models of biological systems. This problem has been addressed by using optimization, Bayesian methods and state observers. I will introduce an approach based on a constrained Hybrid Extended Kalman Filter, together with a chi-squared variance test that allows to assess the reliability of the computed estimates, and to refine them in case they're not accurate enough. The same tools can be used for model selection, in which one has to pick the most likely model for a given process among a list of candidates. I will demonstrate the use of these ideas on two examples, namely the Heat Shock response in E. coli and the Repressilator.