

**UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA**  
**DOTTORATO DI RICERCA IN Tecnologie Convergenti per i Sistemi**  
**Biomolecolari – XLII CICLO**

**Research Topic ID: XLII – 1.12**

**Project Tutor:** Pasquale Palumbo

**Project Supervisor/s:** Marco Vanoni

**Project Title:** Whole-cell models of eukaryotic microorganisms

**Scientific background & Objectives**

Complex biological functions emerge from network-level interactions rather than from the simple sum of molecular activities [1]. Capturing this complexity requires quantitative, dynamical whole-cell models that integrate processes across multiple scales. Following the pioneering whole-cell model of *Mycoplasma genitalium* [2], a major challenge is extending such approaches to eukaryotic microorganisms, including the budding yeast *Saccharomyces cerevisiae*, a key model organism whose essential genes are highly conserved in humans and relevant to cancer and drug discovery [3,4].

This project advances whole-cell modeling of eukaryotes by building on an existing coarse-grained framework integrating metabolism, growth, and cell-cycle regulation in *S. cerevisiae* [5,6]. The candidate will perform large-scale *in silico* experiments under steady-state, perturbed, and varying nutrient availability. Thanks to its modular design, the model can incorporate detailed submodules, such as ribosome biogenesis, genome-scale metabolism, refined cell-cycle control, and signaling pathways, thereby enhancing predictive accuracy and integrative power.

**Project's Networks, Sustainability & Mobility**

- a) the coherence of the suggested project with competences/tools of the hosting lab
- b) intradepartmental or external collaborations
- c) at least one pertinent research article published by the proposer/s
- d) 1 (or more) putative foreign institutions for achieving the required ordinary mobility (6 months)

a) The project is coherent with the competences of the Lab “Post-Genomic Data Analysis and Biological Circuits Modeling”, led by Prof. Palumbo, that include mathematical modelling, reverse engineering, flux balance analysis and data processing

b) Prof. Abhyudai Sing, University of Delaware, expert on mathematical modelling of proliferating cells

c) References [5,6]

d) Collaborations with the labs of Bas Teusink (Systems Biology Lab, Amsterdam Institute of Molecular and Life Sciences (AIMMS), Vrije Universiteit Amsterdam, Amsterdam, the Netherlands, [b.teusink@vu.nl](mailto:b.teusink@vu.nl)) and Matteo Barberis (University of Surrey, United Kingdom, [m.barberis@surrey.ac.uk](mailto:m.barberis@surrey.ac.uk)) are underway

### References

- [1] Bhalla, U.S. & Iyengar, R. Emergent properties of networks of biological signaling pathways. *Science* 283, 381-387 (1999).
- [2] Jonathan Karr et al, A whole-cell computational model predicts phenotype from genotype, *Cell* 2012
- [3] Ferreira R, Limeta A, Nielsen J. Tackling Cancer with Yeast-Based Technologies. *Trends Biotechnol.* 2019;37(6):592–603.
- [4] Nielsen J. Yeast Systems Biology: Model Organism and Cell Factory. *Biotechnol J.* 2019;14(9):e1800421
- [5] P. Palumbo, et al., "An integrated model quantitatively describing metabolism, growth and cell cycle in budding yeast", In M. Pelillo et al., editors, *Artificial Life and Evolutionary Computation*, volume 830, pages 165–180. Springer, 2018
- [6] Vanoni M., Palumbo P. et al A modular model integrating metabolism, growth, and cell cycle predicts that fermentation is required to modulate cell size in yeast populations. *PLOS-CB*, 2025. <https://doi.org/10.1371/journal.pcbi.1013296>