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

Research Topic ID: XL – 1.17

Proponent: Prof. Pasquale Palumbo

Project Title: Whole-cell models of *S. cerevisiae*

Scientific background and 'open issues'

The realization, brought by systems biology, that complex biological functions arise as emergent properties of a network [1,2], and not merely as the sum of the activity of all proteins involved in that network, indicates that the utilization of dynamic molecular models is required at some stage to understand how a genotype interacts with the surrounding environment to produce a given phenotype [3-6]. Computational models are expected to increase the understanding of how complex biological functions arise from the interactions of large numbers of gene products and biologically active low molecular weight molecules. Recent studies underline the need to develop quantitative models of the whole cell in order to tackle this challenge and to accelerate biological discoveries [7-10].

Dealing with whole cell models everything started from the breakthrough paper [11], where a whole-cell model is presented for *M. genitalium* a very basic microorganism (it's a bacterium with only about 500 genes, no signaling pathways and no adaptation to external cues). Now the quest is for eukaryotic whole cell models (like *S. cerevisiae*), much more complex cellular systems since, with respect to *M. genitalium*, they have a compartmentalized cellular organization, a ten-fold larger genome, different signaling pathways, a large set of homeostatic response to external cues and sophisticated nutritionally modulated sensing. Within this framework, many attempts have been carried out, no one yet successfully able to properly describe the emergent properties of complex living organisms arising from the interconnections of the different and diverse biological functions tightly wired within a cell. The project aims at investigating whole cell models for the budding yeast *S. cerevisiae*, a yeast that meets all requirements needed to serve as a eukaryotic model organism: (i) it offers an appropriate fast growth rate, (ii) it is experimentally tractable since it can grow also in minimal media, and (iii) it acts very rarely as human pathogen, therefore it can be handled without any appreciable safety precautions. Last, but not least, investigating the biological mechanisms of yeast cells can also help to understand the general molecular and cellular mechanisms in mammalian cells.

Objectives

The objective of the project is to build up a mathematical whole-cell model including the three main cellular functions: metabolism, growth and cell cycle. The model will be conceived as modular: a scaffold provided by a coarse-grained model interconnecting the above mentioned cellular functions, constituting the bulk for massive population simulations

[12]. Although the integrated model lacks molecular details, it may offer its validated framework to integrate many molecular models of cell subsystems. Therefore, different plug-ins constituted by molecular models describing specific sub-modules of the whole-cell model in as much details as required will be considered: one plug-in is already available, it consists of the G1/S transition molecular module [13], and has already provided excellent results; others may include already existing molecular modules such as the onset of DNA replication [14]. Efforts will also be devoted to conceive molecular blow-ups for yet unmodeled plug-ins, such as the ribosome assembly.

Methodologies

The project benefits of an available scaffold model, already integrating metabolism, growth, and cycle as a coarse-grain model for *S. cerevisiae*, that proved to be extended to the molecular details of the specific blow-up for the G1/S transition [12]. From the one hand, the Ph.D candidate will shard the main cellular activities into functional modules, each conceived as a part of a dense network of interconnected systems. From the other hand, she/he will select a part of these input/output modules providing as many details as possible available from the literature. Within this framework, challenges are gigantic since we need to account for different time-scales, different layers, different levels of granularity, different kinds of data (steady-state/time-series measurements, interactomics, metabolomics, proteomics, etc.). Accordingly, the Ph.D candidate will employ different mathematical tools in order to capture the emergent properties of the cell. To this end both deterministic and stochastic approaches will be followed: the former accounting for average molecules concentrations; the latter accounting for the intrinsic stochasticity inherent to a specific reaction or behavior. Quasi steady-state approximations will be exploited to unburden the computational load emerging from massive populations dynamics including hundred of thousands of cells. The qualitative behaviour analysis will provide properties of the model before numerical simulations or experiments.

Project's Sustainability & Mobility

The project is coherent with the competences of the Lab "Analisi Dati Post-Genomici e Modellistica Circuiti Biologici", that include mathematical modelling, reverse engineering, flux balance analysis and data processing.

Refer to [12,13] for a selection of the proposers' publications related to the project.

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

References

[1] Bhalla, U.S. & Iyengar, R. Emergent properties of networks of biological signaling pathways. Science 283, 381-387 (1999).
[2] Alberghina, L. & Westerhoff, H.V. Systems biology: definitions and perspectives. (Springer, 2005).

[3] Walpole, J., Papin, J.A. & Peirce, S.M. Multiscale computational models of complex biological systems. Annu Rev Biomed Eng 15, 137-154 (2013).
[4] Deisboeck, T.S., Wang, Z., Macklin, P. & Cristini, V. Multiscale cancer modeling. Annu Rev Biomed Eng 13, 127-155 (2011).
[5] Eissing, T. et al. A computational systems biology software platform for multiscale modeling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks. Front Physiol 2, 4 (2011).
[6] Kitano, H. Grand challenges in systems physiology. Front Physiol 1, 3 (2010).
[7] I.E. Elsemman et al, Whole-cell modeling in yeast predicts compartment-specific proteome constraints that drive metabolic strategies, Nat. Comm, 13:801, 2022
[8] T.A. Ahn-Horst, et al, An expanded whole-cell model of E. coli links cellular physiology with mechanisms of growth rate control, Systems Biology and Applications (2022) 8:30
[9] S.O. Adler et al, A yeast cell cycle model integrating stress, signaling, and physiologyFEMS Yeast Research, 22, 2022
[10] M. Barberis, P. Verbruggen, Quantitative Systems Biology to decipher design principles of a dynamic cell cycle network: the “Maximum Allowable mammalian Trade–Off–Weight” (MAmTOW), Systems Biology and Applications (2017) 3:26 ; doi:10.1038/s41540-017-0028-x
[11] Jonhatan Karr et al, A whole-cell computational model predicts phenotype from genotype, Cell 2012
[12] P. Palumbo, M. Vanoni, F. Papa, S. Busti, M. Wortel, B. Teusink, L. Alberghina, 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.
[13] Palumbo, P. et al. Whi5 phosphorylation embedded in the G1/S network dynamically controls critical cell size and cell fate. Nat Commun 7, 11372 (2016).
[14] Brummer, Salazar, Zinzalla, Alberghina and Hoefer, PLoS Comput. Biol. 6, e1000783, 2010