Prediction of Drug Targets in Human Pathogens

Rita Silvério-Machado[1], Miguel Rocha[2], Carlos J. V. Simões[3], Rui M.M. Brito[3,4], Bráulio R.G.M. Couto[5], Marcos A. Dos Santos[6]

1. Institute of Biological Sciences, Federal University of Minas Gerais,Belo Horizonte, MG 31270-901, BR
2. Centre of Biological Engineering (CEB), School of Engineering, University of Minho, Campus de Gualtar, Braga, PT
3. BSIM2, Biocant Park, 3060-197 Cantanhede, PT
4. Center for Neuroscience and Cell Biology, University of Coimbra, 3004-517 Coimbra, PT
5. Centro Universitário de Belo Horizonte/UNI-BH, Belo Horizonte, MG 30455-610, BR
6. Department of Computer Science, Federal University of Minas Gerais,Belo Horizonte, MG 31270-901, BR

The identification of new and "druggable" targets in bacteria is a critical endeavour in pharmaceutical research of novel antibiotics to fight infectious agents. The rapid emergence of resistant bacteria makes today's antibiotics more and more ineffective, consequently increasing the need for new pharmacological targets and novel classes of antibacterial drugs.

A new model that combines the singular value decomposition technique with biological filters comprised of a set of protein properties associated with bacterial drug targets and similarity to protein-coding essential genes of E. coli has been developed to predict potential drug targets in the Enterobacteriaceae family [1]. This model identified 99 potential target proteins amongst the studied bacterial family, exhibiting eight different functions that suggest that the disruption of the activities of these proteins is critical for cells.

Out of these candidates, one was selected for target confirmation. To find target modulators, receptor-based pharmacophore hypotheses were built and used in the screening of a virtual library of compounds. Post-screening filters were based on physicochemical and topological similarity to known Gram-negative antibiotics and applied to the retrieved compounds. Screening hits passing all filters were docked into the protein's catalytic groove and 15 of the most promising compounds were purchased from their chemical vendors to be experimentally tested in vitro.

To the best of our knowledge, this is the first attempt to rationalize the search of compounds to probe the relevance of this candidate as a new pharmacological target.

[1] Silverio-Machado, R., Couto, B.R. and Dos Santos, M.A. (2015) Retrieval of Enterobacteriaceae drug targets using singular value decomposition.   Bioinformatics, 31, 1267-1273.

Encontro de Jovens Investigadores de Biologia Computacional Estrutural
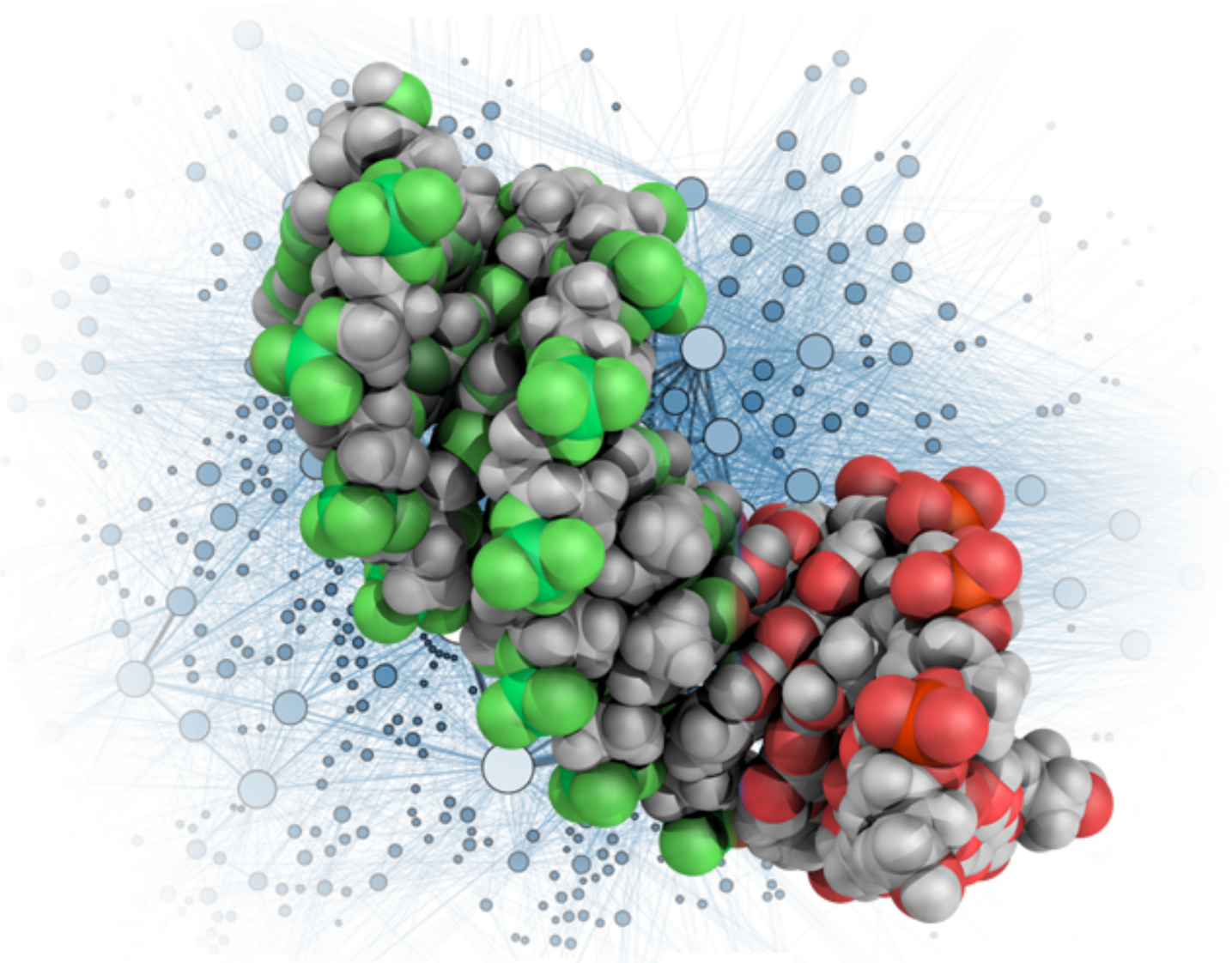
Instituto Pedro Nunes
Coimbra, 18 de Dezembro de 2015