PhD in computational biology

Title : Multi-objective evolutionary algorithms for the identification of master regulators in pancreatic cancer

Laboratories: Institute of Biology Valrose (iBV), laboratory of Computer Science, Signals and Systems (I3S)

Supervision: Olivier Soriani (iBV, olivier.soriani@unice.fr), Claude Pasquier (I3S, claude.pasquier@unice.fr)

Location: Sophia Antipolis, France.

Starting date : December 2017

Duration : 3 years

Context

The PhD position is funded by the UCAJEDI Research program UCAncer (modeling the plasticity of cancer stem cells: from fundamental mechanisms to novel bioactive molecules). The successful applicant will work at the interface between two collaborating research teams : one from the Institute of Biology Valrose (iBV), team 1: Dr Olivier Soriani and the other from the laboratory of Computer Science, Signals and Systems (I3S), team 2: Dr Claude Pasquier. The project combines computer science, cell biology and in vivo approaches to build and validate the functional network associated to stroma-induced cancer cell electrical plasticity.

In this project, the proposed PhD position will focus on the elaboration of optimization algorithms that can identify, from a large amount of biological measures, the network of ion transport-associated proteins involved in the progression of pancreatic cancer.

Project description

PDAC, with a 5-year survival below 6% represents the most fatal disease among solid cancers and a public health priority. Presence of a prominent non-cancerous cell compartment within the tumor (a main characteristic of PDAC) is directly affecting patient clinical outcomes. In PDAC, the most aggressive cells are isolated and selected by a poorly vascularized fortress of stromal cells, mainly composed of cancer-associated fibroblasts (CAF) (Omary et al., 2007). Stromal and cancerous compartments entertain a dynamic crosstalk reinforcing cell aggressiveness potency. Therefore, characterization of the molecular effectors orchestrating this crosstalk may open new therapeutic windows targeting inter cellular communications (Leca et al., 2016). As membrane cell biosensors, ion channels are potential players of the crosstalk between cancer cells and the tumor micro-environment (see the work of team 1: Crottes et al., 2016; Guiguinou et al, 2017; Rapetti-Mauss et al., 2017). The question of the global remodeling of the cancer cells "electrical signature" during the crosstalk with stromal cells and its consequences on tumorigenesis and metastasis onset have not yet been addressed.

Our project proposes to explore, through bioinformatics approaches, the therapeutic potential of the ion channels (membrane proteins defining cell electrical signature) involved in the progression of pancreatic ductal adenocarcinoma (PDAC), and most specifically in the crosstalk between stromal and cancer epithelial cell compartments.

Hypothesis: Team 1 has observed that inputs from the stroma provoke a remodeling of ion channel expression in cancer cells. This electrical plasticity in turn influences cancer cell phenotype and early steps of metastasis progression. Targeting master regulators of electrical plasticity may be a strategy to disable the crosstalk between compartments to decrease metastatic progression and restore sensitivity to reference treatments. For this purpose, team 1 will quantify the transcript levels by RNA-Seq and the proteome by mass spectrometry for both control PDAC cells and stroma-stimulated cells.

The major regulators are expected to belong to the set of molecules exhibiting important variation between the two conditions (criterion 1). However, this criterion alone is not sufficient because it will favor a selection based only on molecules with the greatest variation. An effective selection method usually refines the selection by taking into account the implication of the molecules in the process under study (criterion 2) and their connexions in biological networks represented as directed graph (criterion 3).

Team 2 envision to tackle the problem not as successive filtering tasks but as an optimization problem taking into account all criteria at the same time. This problem is characterized by a highly complex search space (potentially 2^n solutions where n is the number of measures; of the order of several thousand) and possibly conflicting objectives.

Task: We are looking for a smart and motivated student to investigate computational methods allowing selecting the key molecules involved in cancer progression. The first task of the selected candidate will be to properly define evaluation functions (which measure the goodness of the selected features) for all the criteria. By relying on previous work performed in team 2 (Pighetti et al. 2015), he will handle the problem as a multi-objective feature selection problem by using evolutionary computation (EC). He will investigate solutions hybridizing EC and a classification algorithm (i.e. SVM). Unlike previous work performed in team 2, the candidate will adopt an approach using multi-objective genetic programming (GP) because of its ability to deal with features having intrinsic linkages and to reveal these relationships (Xue et al. 2016).

The candidate will work in team 2 and he is going have many interactions with team 1 that will validate the selected proteins by evaluating the impact of their invalidations on the response of cancer cells to stimulation by the stroma. Results of this evaluation will be used to refine the method.

Candidate profile

The candidate must have a Master or equivalent in computer science, bioinformatics or biology. He should ideally have a strong background in computer science (good programming skills, knowledge of evolutionary computation) and a good knowledge in molecular biology (knowledge in the processing of RNA-Seq and mass spectrometry data). The candidate must be fluent in english.

Application

Send by email a CV, a cover letter, 1 or 2 recommendation letters to claude.pasquier@unice.fr and olivier.soriani@unice.fr

References

Crottes, D., Rapetti-Mauss, R., Alcaraz-Perez, F., Tichet, M., Gariano, G., Martial, S., Guizouarn, H., Pellissier, B., Loubat, A., Popa, A., et al. (2016). SIGMAR1 Regulates Membrane Electrical Activity in Response to Extracellular Matrix Stimulation to Drive Cancer Cell Invasiveness. Cancer Res 76, 607-618

Leca, J., Martinez, S., Lac, S., Nigri, J., Secq, V., Rubis, M., Bressy, C., Serge, A., Lavaut, M.N., Dusetti, N., et al. (2016). Cancer-associated fibroblast-derived annexin A6+ extracellular vesicles support pancreatic cancer aggressiveness. The Journal of clinical investigation

Rapetti-Mauss R, Bustos V, Thomas W, McBryan J, Harvey H, Lajczak N, Madden SF, Pellissier B, Borgese F, Soriani O*, Harvey BJ*. Bidirectional KCNQ1:β-catenin interaction drives colorectal cancer cell differentiation. Proc Natl Acad Sci U S A. 2017 Apr 18;114(16):4159-4164.

Soriani O, Rapetti-Mauss R. Sigma 1 Receptor and Ion Channel Dynamics in Cancer. Adv Exp Med Biol. 2017;964:63-77.

Gueguinou M, Crottès D, Chantôme A, Rapetti-Mauss R, Potier-Cartereau M, Clarysse L, Girault A, Fourbon Y, Jézéquel P, Guérin-Charbonnel C, Fromont G, Martin P, Pellissier B, Schiappa R, Chamorey E, Mignen O, Uguen A, Borgese F, Vandier C, Soriani O. The SigmaR1 chaperone drives breast and colorectal cancer cell migration by tuning SK3-dependent Ca(2+) homeostasis. Oncogene. 2017 Jan 23.

Pighetti, R., Pallez, D., Precioso, F. (2015). Improving SVM Training Sample Selection Using Multi-Objective Evolutionary Algorithm and LSH. IEEE Symposium Series on Computational Intelligence, SSCI 2015: 1383-1390.

Xue, B., Zhang, M., Browne, WN., Yao, X. (2016). A Survey on Evolutionary Computation Approaches to Feature Selection. IEEE Trans Evol Comput, 20:606–626.