Research Internship M2, 2017

Title : Identification of master regulators in pancreatic cancer using evolutionary algorithms

Laboratory : SPARKS, laboratoire I3S (CNRS-UNS-UCA)

Location : Sophia Antipolis, France.

Supervision : Claude Pasquier (I3S, claude.pasquier@unice.fr) & Denis Pallez (I3S, denis.pallez@unice.fr), in collaboration with Olivier Soriani (iBV, olivier.soriani@unice.fr)

Starting date : ASAP

Duration : 6 months

Financing : around 550 euros / month

Candidate profile : student in computer science, bioinformatics or biology with a specialization in computer science

PhD opportunity : Yes

Context

Pancreatic ductal adenocarcinoma (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 is directly affecting clinical outcomes. In PDAC, the most aggressive cells are isolated and selected by a poorly vascularized fortress of stromal cells (cancer-associated fibroblasts, CAF) (Omary et al., 2007). Moreover, 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 (Crottes et al., 2016), but their therapeutic potency is still largely underestimated and has not been addressed in PDAC so far. 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.

We have observed, using CAF from patients, 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 more particularly epithelial to mesenchymal plasticity, an early step 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.

We plan to design a system allowing to highlight control channel networks of disturbed signaling pathways involved in cancer cell phenotype. The main regulators will be selected among those exhibiting an altered expression between control PDAC cells and CAF-stimultated cells (criterion

1), that are involved in epithelial-mesenchymal plasticity (criterion 2) and that affect biological pathways at both transcriptomic and proteomic level (criteria 3 & 4).

The fulfillment of criterion 1 consists in selecting a subset of transcripts or proteins that maximize the performance of a classification model discriminating control PDAC cells and CAF-stimulated cells. Criterion 2 promotes the selection of molecules whose annotations (by controlled vocabularies and ontologies) provide a number of evidence about their involvement in cancer cell phenotype. Criteria 3 & 4 highlight set of molecules which hold important status on interaction networks; because of their high connectivity, their involvement in important modules or their action on channel networks associated with the phenotype.

This problem is characterized by a highly complex search space (potentially 2^n solutions where n is the number of measures) and possibly conflicting objectives.

The problem will be handled as a multi-objective feature selection problem by using evolutionary computation (EC). By relying on previous work performed in the team (Pighetti et al. 2015 ; Pighetti 2016), the candidate will develop a system hybridizing EC and a classification algorithm (i.e. SVM). In a second step, he will improve the method by merging EC and the classification task using Genetic Programming (GP). Indeed, the interest of GP is its ability to be used both as a multi-objective search algorithm and as a classification algorithm (Xue et al., 2016).

The software developments will be based on the ECJ Evolutionary Computation Toolkit (http://cs.gmu.edu/~eclab/projects/ecj/).

Candidate profile

The candidate should ideally have a background computer science and biology. He must be experienced in Java programming. A background and/or a strong interest in cell biology and evolutionary computation are strong advantages.

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

Omary, M.B., Lugea, A., Lowe, A.W., and Pandol, S.J. (2007). The pancreatic stellate cell: a star on the rise in pancreatic diseases. JClinInvest 117, 50-59.

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.

Pighetti R. (2016). Content-Based Information Retrieval combining evolutionary algorithms and SVM, PhD thesis.

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.