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# COMBINATION THERAPIES AND DRUG RESISTANCE IN HETEROGENEOUS TUMORAL POPULATIONS

Elena Piretto[1,2]*, Marcello Delitala[1] and Mario Ferraro[3]

[1]Politecnico di Torino, Dipartimento di Scienze Matematiche,
corso Duca degli Abruzzi 24, 10129 Torino, Italy;

[2]Università degli studi di Torino, Dipartimento di Matematica,
via Carlo Alberto 10, 10123 Torino, Italy;

[3]Università degli Studi di Torino, Dipartimento di Fisica,
via P. Giuria 1, 10125 Torino, Italy.

elena.piretto@polito.it (*corresponding author), marcello.delitala@polito.it, ferraro@ph.unito.it

The idea that cancer as an evolutionary disease is nowadays commonplace. Indeed cancer development is driven by mutation and selective forces, among them the action of immune system, interspecific competition and therapies. In recent years, the frontiers for medical treatments have been represented by the double blind combination therapies which aim to combine the effect of different drugs affecting different hallmarks of cancer, in order to reduce the emergence of resistance (and unresponsiveness) after multiple treatments.

The aim of this talk is to present a mathematical model which can act as an silico laboratory, providing some insights on the effectiveness of therapies in relation with the competition among the cancer populations. Set in the framework of cancer ecology and population dynamics, the model consists of two cancer subpopulation competing for resources and "preyed upon" by immune system cells. The effects of therapies, adding further selective pressure to the ecosystem, are next taken into account.

Numerical simulations have been performed to analyze the effects of different doses and schedules of treatments, used singly or in combination, especially as concern resistance to drugs. General results of the simulation have been then applied non-small cell lung cancer, and clinical protocols have been tested. Finally, comparisons with some experimental data provide some suggestions on the effectiveness of therapies and how to reduce the development of drug resistance.

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