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colloquia@iasi

"La mente è come un paracadute.
Funziona solo se si apre"
A. Einstein

Driver and passenger mutations in transition from inborn neutropenia to AML

Prof. **Marek Kimmel**
Department of Statistics and Bioengineering, Rice University, Houston, TX (USA)

Abstract

Transition from severe congenital neutropenia (SCN) to myelodysplastic syndrome (MDS) to acute myeloid leukemia (AML) provides a unique opportunity to study accumulation of driver and passenger mutations in carcinogenesis. We use the mathematics of multitype branching process and of the Moran model. Based on the former, we derive equations for the distributions of the times to consecutive driver mutations and set up simulations involving a range of hypotheses regarding acceleration of the mutation rates in successive mutant clones. Our model reproduces the clinical distribution of times at diagnosis of secondary AML. Surprisingly, within the framework of our assumptions, stochasticity of the mutation process is incapable of explaining the spread of times at diagnosis of AML in this case; it is necessary to additionally assume a wide spread of proliferative parameters among disease cases. For the second part of the talk, we study the time to fixation of the Delta 715 mutant of the GCSF receptor under several versions of the Moran model, in an attempt to understand the transition kinetics to the MDS stage. We also comment on the relationships between branching processes and Cannings, Wright-Fisher and Moran models.

Contributions of Seth Corey, Taly Glaubach and Tomasz Wojdyla are thankfully acknowledged.