Mini-course CMAP EP Fall 2024

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Discrete Population Models Inspired by Applications in Cancer Research

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Synopsis

Mutation, genetic drift and selection in proliferating cancer cells lead to populations with highly diversified genomes and complicated dynamics. Mathematical tools to describe the resulting stochastic phenomena are classical population genetics models such as Wright-Fisher and Moran Models, as well as branching processes (bp) and more general Markov processes. Diversity of cells and genomes frequently leads to models with infinite collections of types. This mini-course comprises a review of several such models, preceded by a capsule introduction into cancer dynamics including certain statistical issues such as early detection paradoxes, followed by a brief review of mathematical tools. The exposition will be mathematically elementary, with emphasis on intuitions and model building, but examples of mathematical proofs and reference to the body of published literature will be provided.

The general aim is to inspire interest in the field which is currently rapidly expanding and has a lot of interesting connections with basic processes in living cells. Although these are biologically and mathematically diverse models, they share some "exotic" properties, which result from nontrivial interaction between cell growth and type transitions.

Meeting 1: Biological and mathematical background

- DNA, RNA, and proteins, and the dogma of molecular biology, structure of human genomes
- quantitative theories of cancer
- models of population genetics
  - genetic drift: time-continuous Moran model vs. time-discrete Wright-Fisher model
  - mutations: infinite alleles and infinite sites models
  - neutral evolution and the coalescent
- branching processes
  - Galton-Watson (GW) process: basic pgf equations and criticality, Yaglom Theorem
  - time-continuous processes and two-type Goldie-Coldman bp model of drug resistance

Meeting 2: Gene amplification. Role of quasi-stationarity

Amplification of a gene is an increase of the number of copies of that gene in a cell. Amplification of genes coding for the enzyme dihydrofolate reductase (DHFR) has been associated with cellular resistance to the anticancer drug methotrexate (MTX).

We will define and analyze a GW branching process-based model of stochastic dynamics of DHFR gene. Using the sub-critical GW process, the model reproduces the rate and pattern of evolution of resistance and decay of

resistance after removal of the selective agent and explains . This follows from the classical Yaglom's theorem on subcritical GW conditional on non-extinction (a form of quasistationarity).

Furthermore, we will discuss other related models including a time continuous branching random walk and branching within branching.

Meeting 3: Telomere dynamics, from branching random walk to Greiner's model

Telomeres are specialised non-coding double-stranded repetitive DNA-protein complexes that form protective caps on the ends of chromosomes. Eventually cells will acquire critically short and dysfunctional telomeres that, consequently, activate a DNA damage response and growth arrest known as replicative senescence. Therefore, all somatic cells have limited cell proliferation capacity called the Hayflick limit.

We review mathematical models of telomere dynamics, many of which have the form similar to branching random walks or queuing systems. In addition, we discuss some possible approaches based on recent progress in molecular biology of cell replication.

In addition, we discuss the connection between telomere loss, immortalization of cancer cells and chromosome missegregation in cancer. The subject is related to the branching within branching model and its refinements.

Meeting 4: Heavy-tail distributions in cell proliferation models

Recent progress in microdissection and in DNA sequencing has facilitated the subsampling of multi-focal cancers in organs such as the liver in several hundred spots, helping to determine the pattern of mutations in each of these spots. This has led to the construction of genealogies of the primary, secondary, tertiary, and so forth, foci of the tumor. These studies have led to diverse conclusions concerning the Darwinian (selective) or neutral evolution in cancer. Mathematical models of the development of multi-focal tumors have been devised to support these claims.

We consider a model for the development of a multifocal tumor: it is a mathematically rigorous refinement of a model of Ling et al. (2015). Guided by numerical studies and simulations, we show that the rigorous model, in the form of an infinite-type branching process, displays distributions of tumor size which have heavy tails and moments that become infinite in finite time. In addition to its inherent mathematical interest, the model is corroborated by recent literature on apparent super-exponential growth in cancer metastases.

Meeting 5: Tug-of-War model of competition between advantageous and deleterious mutations

We consider a time-continuous Markov branching process of proliferating cells with a countable collection of types. Among-type transitions are inspired by the Tug-of-War process introduced by McFarland et al (2014) as a mathematical model for competition of advantageous driver mutations and deleterious passenger mutations in cancer cells. A follow-up biological study by McFarland and co-authors in 2017 showed that passenger mutations are mildly deleterious and might inhibit or reverse tumour growth. In their experiment, authors discovered that passengers are capable to reduce proliferative fitness, slow tumour growth, and reduce metastasis progression.

We introduce a version of the model in which a driver mutation pushes the type of the cell L-units up, while a passenger mutation pulls it 1-unit down. The distribution of time to divisions depends on the type (fitness) of cell, which is an integer. The extinction probability given any initial cell type is strictly less than 1, which allows us to investigate the transition between types (type transition) in an infinitely long cell lineage of cells. The analysis leads to the result that under driver dominance, the type transition process escapes to infinity, while under passenger dominance, it leads to a limit distribution. Implications in cancer cell dynamics and population genetics are discussed.

Meeting 6: To be determined