Minisymposium 18
Stochastic processes of mutation, selection and growth in cancer: models and data (Marek Kimmel, organizer)

Tuesday, June 17, 2104

11.40 – 12.20 Alexandra Jilkine, Notre Dame University, **Mathematical models of stem cell renewal and dedifferentiation**

12. 20 – 13.00 Thomas McDonald, Rice University, **A multitype infinite-alleles Galton Watson process and applications to cancer evolution**

13.00 – 14.00 Lunch

14.10 – 14.50 Tomasz Wojdyla, Silesian University of Technology **Cancer evolution model based on the Moran model with selection and co-localization**

14.50 – 15.30 Cristian Tomasetti, Johns Hopkins University, **New findings on cancer via stochastic modeling and statistical analysis**

Abstracts

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Mathematical models of stem cell renewal and dedifferentiation.

Recent evidence suggests that, like many normal tissues, many cancers are maintained by a small population of cancer stem cells that divide indefinitely to produce more differentiated cancerous cells. Tissues, however, contain many more differentiated cells than stem cells, and mutations may cause such cells to ``dedifferentiate'' into a stem-like state.
We study the effects of dedifferentiation on the time to cancer onset and found that the effect of dedifferentiation depends critically on how stem cell numbers are controlled by the body. If homeostasis is very tight (due to all divisions being asymmetric), then dedifferentiation has little effect, but if homeostatic control is looser (allowing both symmetric and asymmetric divisions), then dedifferentiation can dramatically hasten cancer onset and lead to exponential growth of the cancer stem cell population.
We consider both space-free and spatial versions of this process to look at effect that tissue architecture can play in this process. Our results suggest that dedifferentiation may be a very important factor in cancer and that more study of dedifferentiation and stem cell control is necessary to understand and prevent cancer onset.

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A multitype infinite-alleles Galton Watson process and applications to cancer evolution

The infinite-allele Galton Watson process proposed by Griffiths and Pakes is extended to a multitype process allowing for different types and labels. The process allows the offspring to be of a different type according to the parent probability generating function or be a new label with a given probability, μ. In this case, types are distinguishable in each generation. Labels are indistinguishable, but the number of labels can be traced by using the ancestral p.g.f. Limit behavior of the process has been determined, particularly the asymptotic growth of the number of labels for each type and the limit of the frequency spectrum for each type. We show the results based on whether or not the process is reducible to allow us to create a model for evolution, where mutations may be reversible with a negligible probability.
The process has applications to cancer evolution, with different types representing different sets of driver mutations, or mutations that affect the rate of growth of cells. Labels can then represent different sets of passenger mutations that are evolving neutrally. Our asymptotic results show the number of labels grow exponentially along with the total number of individuals, so the number of labels can be considered as a surrogate for age of a particular subclone of cells. This can be used to help determine the order of events in the clonal evolution of a population of cancer cells.

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Cancer evolution model based on the Moran model with selection and co-localization

Severe congenital neutropenia (SCN) is a condition that causes affected individuals to be prone to recurrent infections. It is possible to limit those infections by using recombinant granulocyte colony-stimulating factor (GCSF). Unfortunately, SCN often transforms into secondary myelodysplastic syndrome (sMDS) or acute myeloid leukemia (sAML) and there are well established assumptions that the GCSF contribute to this transformation. It was observed that mutations in the distal domain of the GCSF Receptor (GCSFR, gene name CSF3R) have been isolated from SCN patients who developed sMDS/sAML or patients with de novo MDS (Beekman et al., 2012). The evolution of the cancer is clonal and GCSFR truncation mutants become fixed in the granulocyte progenitor population because of an incremental growth advantage.
Here, we model the evolution of the cancer using discrete and continuous versions of the Moran model with selection (Durret, 2008). In this model, the population of granulocyte precursors is constant and consists of N biological cells, including mutant cells, number of which is variable in time (starting from *i* mutants at the beginning). The mutant has selective

advantage expressed by the relative fitness $r = 1+s > 1$, equal to the ratio of average progeny count of the mutant to that of the wildtype. We also incorporate the colocalization factor to the model - we assume that it is more probable, by a factor of $1+\alpha > 1$, that mutant (wildtype) cell will be replaced by a cell of the same type.
It is recognized that about 70% of SCN patients who developed sMDS will express a truncation mutant GCSFR. Using the model we estimate the probabilities and expected times to the fixation of the mutant cells as well as the number of initial mutant cells leading to fixation. We also study the dynamics of the model and the relationship between fitness and colocalization factors.

REFERENCES

Beekman, R *et al.* (2012). Sequential gain of mutations in severe congenital neutropenia progressing to acute myeloid leukemia. *Blood*, 119: 5071-5077.
Durrett, R. (2008). Probability Models for DNA Sequence Evolution (Probability and Its Applications). *Springer,* 2008.

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New findings on cancer via stochastic modeling and statistical analysis

While mathematical modeling of cancer has a long history, very recent developments in our understanding of this dynamical process due to high throughput sequencing methodologies have allowed us to formulate a more detailed mathematical model of cancer initiation and evolution. In this talk the model will be presented with some of its mathematical results and validated predictions. This work is in collaboration with Bert Vogelstein.