# Physics and Mathematics of Cancer

The program will begin with a series of review lectures on cancer by Arnold Levine. The exact schedule is not yet known, but we expect that the following topics will be addressed during the course of the program:

## Cell Signaling in Cancer Cells and Microenvironment.

Hormonal anti-growth signals couple to signaling pathways, such as ErbB and Wnt that control cell division, cell differentiation, and cell death. The weakened response of cancer cells to hormonal anti-growth signals is a key mechanism in cancer development, which is affected by mutations of key proteins that participate in that pathway. Cancer metastasis may be triggered by expression of proteins like "Snail" that trigger the transformation of epithelial cells to the more motile mesenchymal cells through weakened adhesion. Microenvironment refers to the fact that cancer initiation is very sensitive to the interaction of a cell with the local extracellular matrix and with other cells in the immediate neighborhood. Current theoretical descriptions of signaling pathways like ErbB are enormously cumbersome, involving sometimes hundreds of coupled differential equations. Are there mathematical methods that could help us to better understand the operation of these signaling pathways in an economic and compelling way? How can the influence of the microenvironment be included?

Reviews of cancer and cell signaling can be found at:
http://www.nature.com/cr/focus/cell_signaling.html

## Chromatin and Chromosomal Damage of Cancer Cells.

(Dedicated to the memory of Jonathan Widom.)

Cancer is most commonly viewed as a gradual evolutionary progression, accumulate the multiple mutations over years that are required to drive a cancer towards aggressive growth as will be discussed in topic 5. It has long been known that cancer cells also can

undergo larger-scale chromosomal changes, such as fracture of chromosomes and duplication of chromosomes. It was recently shown that in some cancers, the genome can be shattered into hundreds of fragments in a single cellular catastrophe, wreaking mutational havoc on a massive scale. Errors by the DNA repair machinery in sticking chromosomal parts together promote cancer. Recently, the biophysical descriptions of chromatin structure, of condensation (nucleosomes), and of mechanical forces exerted during cell division has made great strides forward. How can these decriptions be applied to chromosome damage?

Stephens et al.: *Massive Genomic Rearrangement Acquired in a Single Catastrophic Event during Cancer Development.* **Cell**, 2011; 144 (1)

## Continuum Theories and Stochastic Models of Tumor/Tissue Growth. Metabolism.

Theoretical physicists have become increasingly involved in the application of continuum physics and of stochastic process theory to tumor growth and tissue development in general. Cancer invasion of tissue has been described by applying the theory of fingering instabilities in solids and fluids. Fluid mechanics and elasticity theory both have been applied to the study of development of wing morphology in fruit flies. Fluid mechanical descriptions of tissue growth have been applied to cancer metastasis focusing on the concept of homeostatic pressure. The study of the physics of cancer metastasis is right now of particular importance following the proposal that cancer metastasis is not a late-stage product of accumulated mutations but triggered by the activation of an existing cell development program, transforming epithelial cells into mesenchymal cells. Finally, the theory of stochastic processes has been used to describe the invasion of brain tissue by glial tumor cells to the spreading of mutations in growing cell populations (“gene surfing”). How do the thermodynamic gradients - mechano-osmotic stress, chemical and

thermal gradients - compare for different cancer types? How do the gradients relate to spatial variations of gene expression? How do the gradients determine the development of cancer morphology, cancer nucleation and cancer metastasis? An issue currently

under intense study is the singular *metabolism* of cancers. The glycolytic rate of tumor cells can be 200 times higher than those of their normal tissues: the *Warburg effect*. Can the Warburg effect be included in continuum descriptions of tumors?

Markus Basan, Thomas Risler, Jean-François Joanny, Xavier Sastre-Garau, and Jacques Prost, *Homeostatic competition drives tumor growth and metastasis nucleation* HFSP J. **3** 265 (2009)

## Mutations, Micro-evolution, and Multi-Stage Models.

The study of the initiation and progression of cancers has for many years seen an active involvement of applied mathematicians with cancer research who focused on the role of the genome, specifically the relation between the statistics of the accumulation of mutations and cancer progression. Starting from the 1950's, with the work of Doll, statistical models based on random mutation rates were found to account well for the age-specificity of cancer. Recently, the group of Carlo Maley applied evolutionary theory, testing mutations on specific genes such p53, to predict the progression of Barrett's oesophagus to cancer: the more diverse the populations of clones, the more likely the cell was found to progress to cancer. The group of Nowak applied genomic sequencing to the different stages of colorectal cancers and was able to predict the development of malignant tumors from benign tumors.

Despite these successes, many crucial unresolved issues remain in the mathematical description of tumor progression: what is the relative importance of "genetic instability" vs "clonal expansion"? Can genetic instability lead to "mutator" phenotypes ?. Can *group selection* really lead to a population with a statistical distribution of genomes ("quasi-species") that collectively conveys a certain level of *mutational robustness* to the group as a whole ("survival of the flattest")? Is cancer progression dominated by a few key successive mutations (e.g., K-Ras, p53, …) or can a large number of mutations, each producing only a limited increase in cell division rate, be just as important. Finally, *epigenetic* changes in DNA methylation patterns could well be more frequent than genetic mutations, allowing for different adaptive *subpopulations* within a given clonal line.

Jones et al. *Comparative lesion sequencing provides insights into tumor evolution*. Proc Natl Acad Sci U S A. 2008 Mar 18;105(11):4283-8