Problem-based Learning for Bioinformatics

Tracking clonal dynamics in cancer

INSTRUCTOR: ANDREW ROTH

March 11/16 2020

You have just been appointed as the principal investigator of an international initiative to investigate molecular mechanisms of treatment resistance in a very aggressive form of cancer. These tumours show an initial response to a targeted pharmacological agent, but ultimately nearly half of the patients relapse and succumb to their disease. You have at your disposal viable tumour tissues from patients exhibiting sensitive and resistant disease. Your institution has recently recruited an expert in animal models for cancer, in particular with expertise in mouse xenografts. Due to a generous grant, your institution has also installed a fleet of next generation sequencing machines that sits alongside a very capable datacenter for computation. The assignment is to outline a workflow (both computational and experimental) that would:

- Aim to determine the genetic underpinnings of treatment resistance
- Identify new targets for novel therapies in treatment resistance tumours
- Design experiments and develop methods to determine the relative fitness of clones under therapeutic selective pressures

This would include the necessity to:

- Inventory ways in which (all forms of) somatic mutations could be determined in cancer focused sequencing studies
- Identify experimental and computational approaches that could quantify how the genotype composition of a population of cells might change in response to chemotherapy
- Identify software or algorithmic approaches that might identify alternative drugs that could be administered to non-responders to standard of care chemotherapy in light of knowing the mutations present in a genome
- Distinguishing stochastic vs deterministic effects of drug selection
- Modeling growth trajectories of clones as an indicator of fitness
- Determine whether properties of resistance are encoded in the genomes of clones, or rather through non-genomic mechanisms.

Stop Press: A colleague from Europe calls you and tells you that they have just invented a method of sequencing the genomes and transcriptomes of individual cells. How could you leverage this new technology in your study?

Discussion Questions

What types of genomic aberrations can be determined by whole genome shotgun sequencing?

How can one use all mutations in a genome to determine those that might be under evolutionary selection?

Why is single molecule sequencing (or methods that approximate it using digital representation of alleles) so relevant to the problem of determining clonal evolution in response to chemotherapy? Why could this not be done with capillary based sequencing? What is intra-tumoural heterogeneity and how is it relevant to the problem of chemotherapeutic resistance?

In solid tumours, a major confounding problem in interpreting alleles from sequencing data is that tumour samples are admixed with normal cells. Think about how this affects your ability to interpret results. How could the level of admixture be measured? Can this idea be extended to quantify the number of clonal populations in the tumour?

What selective pressures are imposed when human tumour tissues are engrafted into mice? How could this impact the interpretation of your results?

What is the relevance and importance of single cell (single nucleus) sequencing methods in understanding clonal dynamics?

How does one elucidate stochastic vs deterministic effects?

What is drift and how does it relate to your problem?

How can we use the theoretical principles of evolution and population genetics to help us tackle this problem?

What is fitness? How can the principles of fitness landscapes be leveraged in this study?

How can time-series modeling be used to resolve clones under selection?

What are the limitations of single cell sequencing?

How can the fact that the patient population is composed of those that respond to treatment and those that don't be leveraged in your experimental design and analysis?