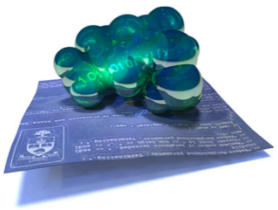
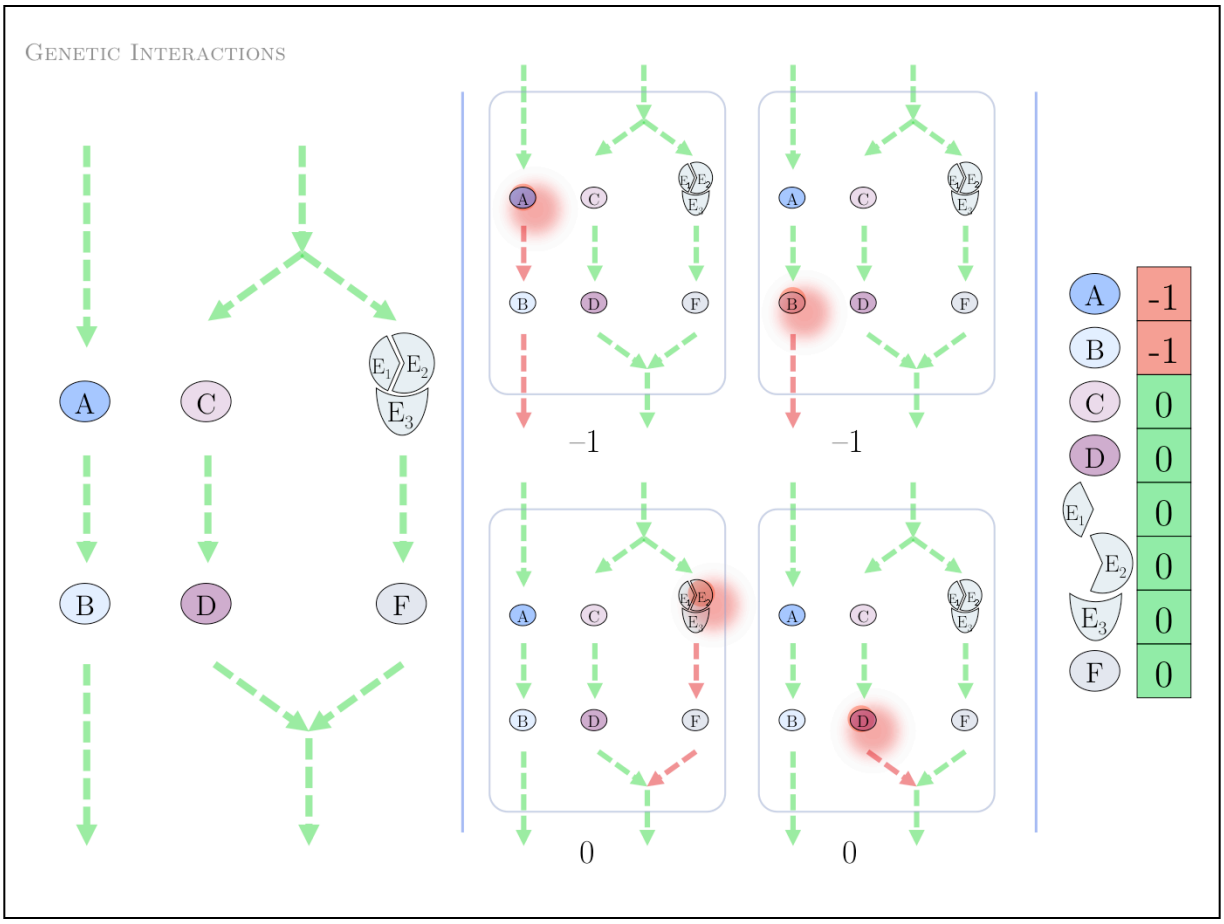
A
Bioinformatics
Course

Physical vs. Genetic Interactions



Boris Steipe

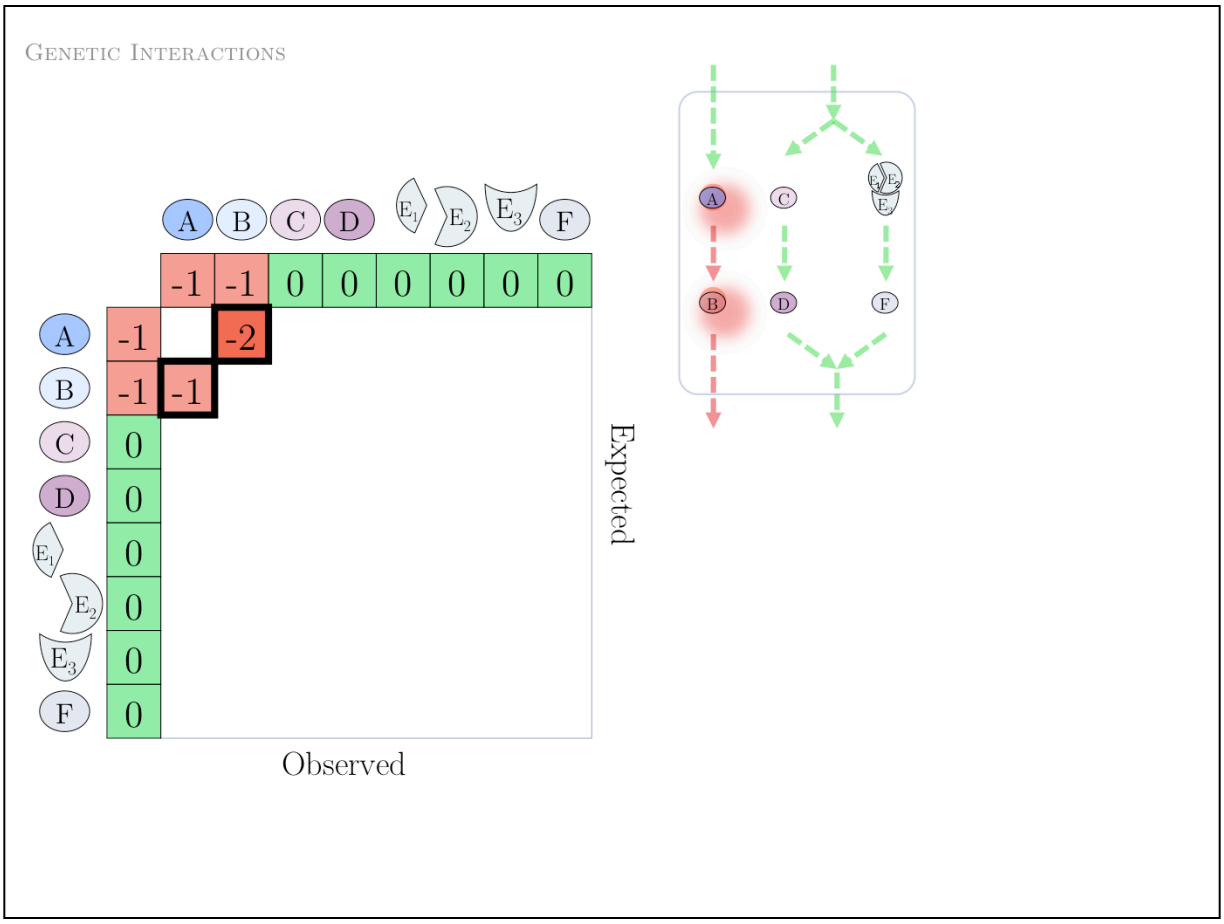
department of biochemistry – department of molecular genetics
University of Toronto



Genetic interaction experiments can map functional interactions. Consider the situation above, in which six proteins are part of two independent pathways. One pathway is formed from the activity of proteins A and B, and one pathway either from C and D, or as a parallel pathway with an $E_{1\text{-}3}$ complex and a protein F.

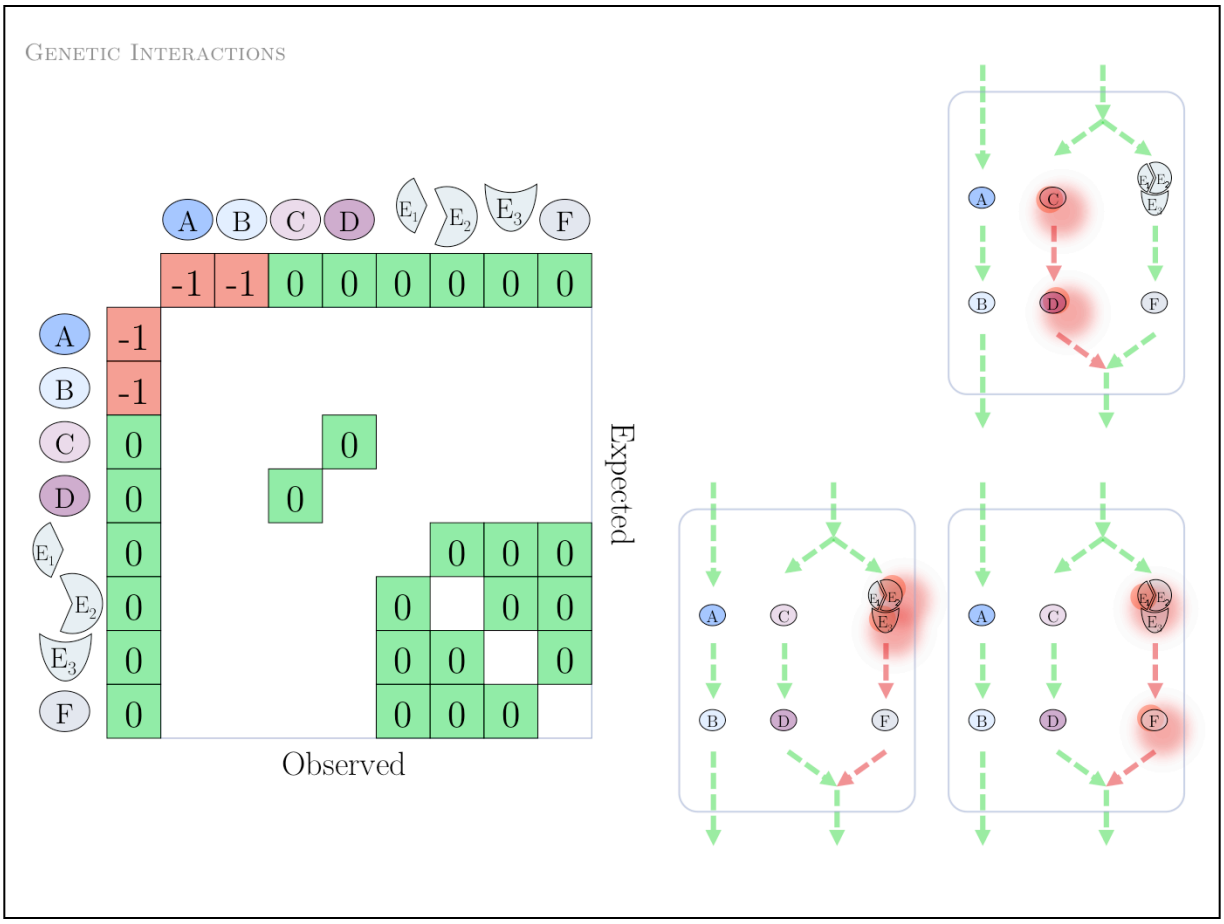
Deleting A or B disrupts the left-hand pathway and leads to a deleterious phenotype, –1, (red).

Deleting any of the other proteins disrupts only one branch of the right-hand pathway and no phenotype is observed: 0 (green).

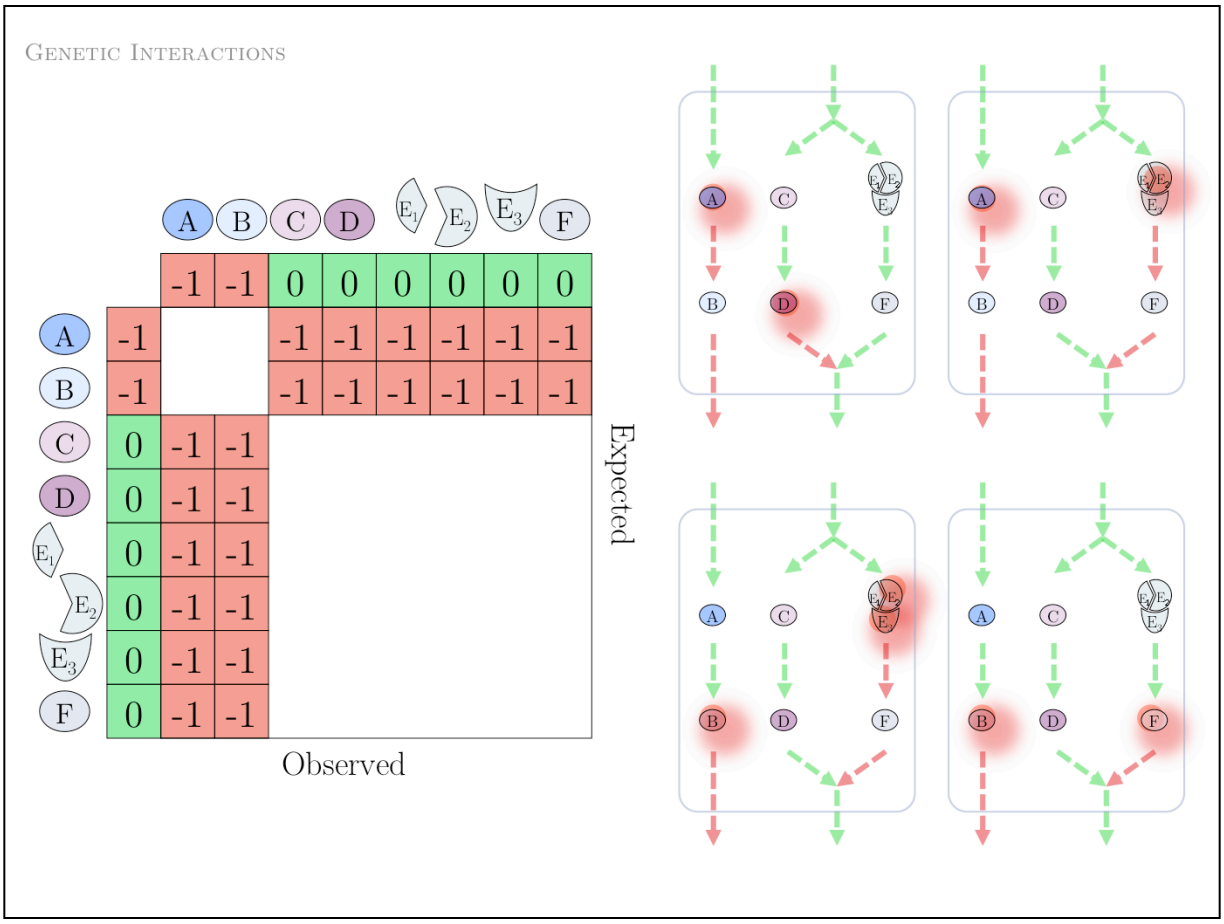


The question then becomes: what happens when we combine those deletions. Each combination of deleting a protein i and a protein j is interpreted as an (i, j) "interaction".

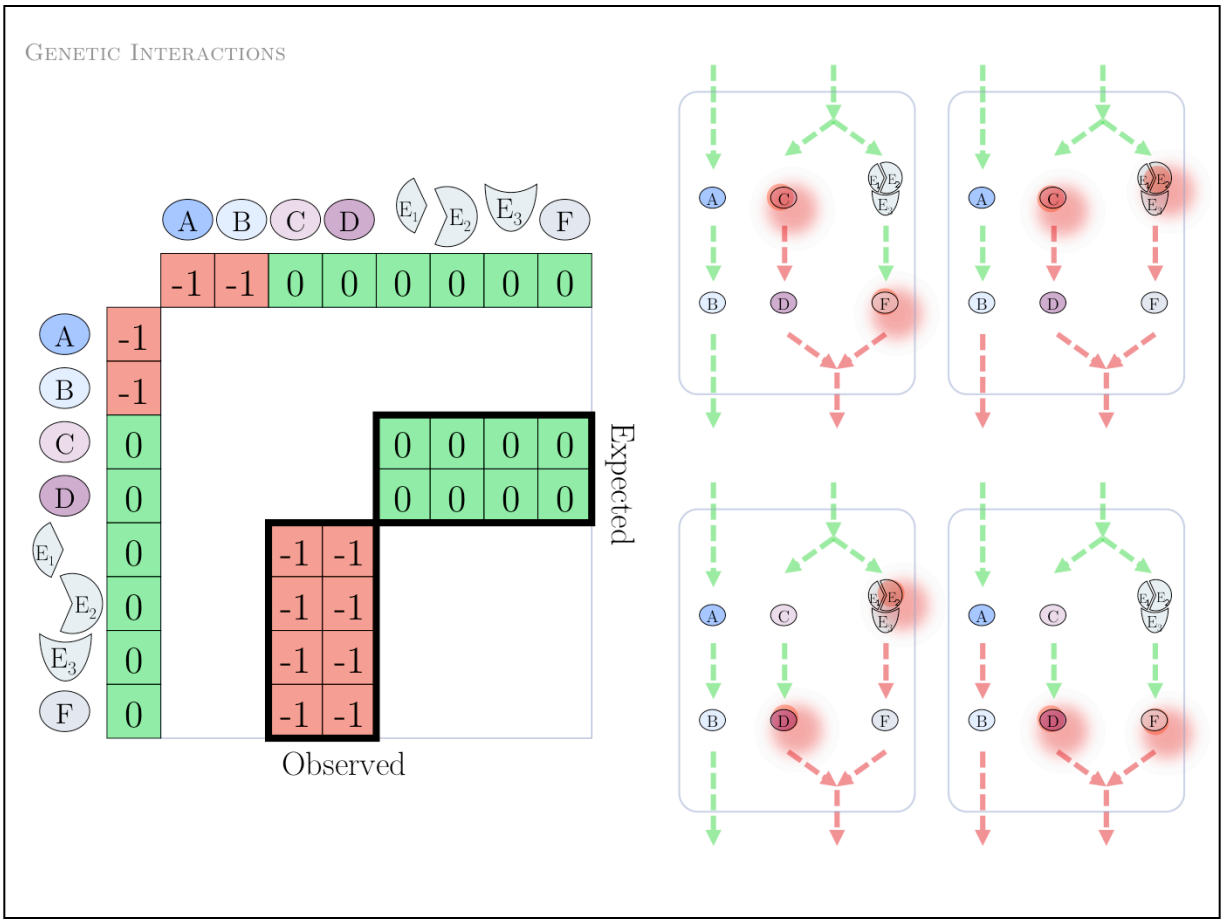
A and B individually have a –1 phenotype. We *expect* a –2 phenotype if they are both introduced into the cell. But we only *observe* a –1. Interrupting the left-hand pathway in two positions deletes it no more profoundly than interrupting it at either A or B. In this case, the observed phenotype is less than what additivity would predict; we call this a positive interaction, a suppressor, or an "epistatic" interaction.



In the same way combinations of mutations in the same branch of the right-hand pathway show no effect. In this case however, since there was originally no effect, we see no difference from the deletions. These are neutral interactions.

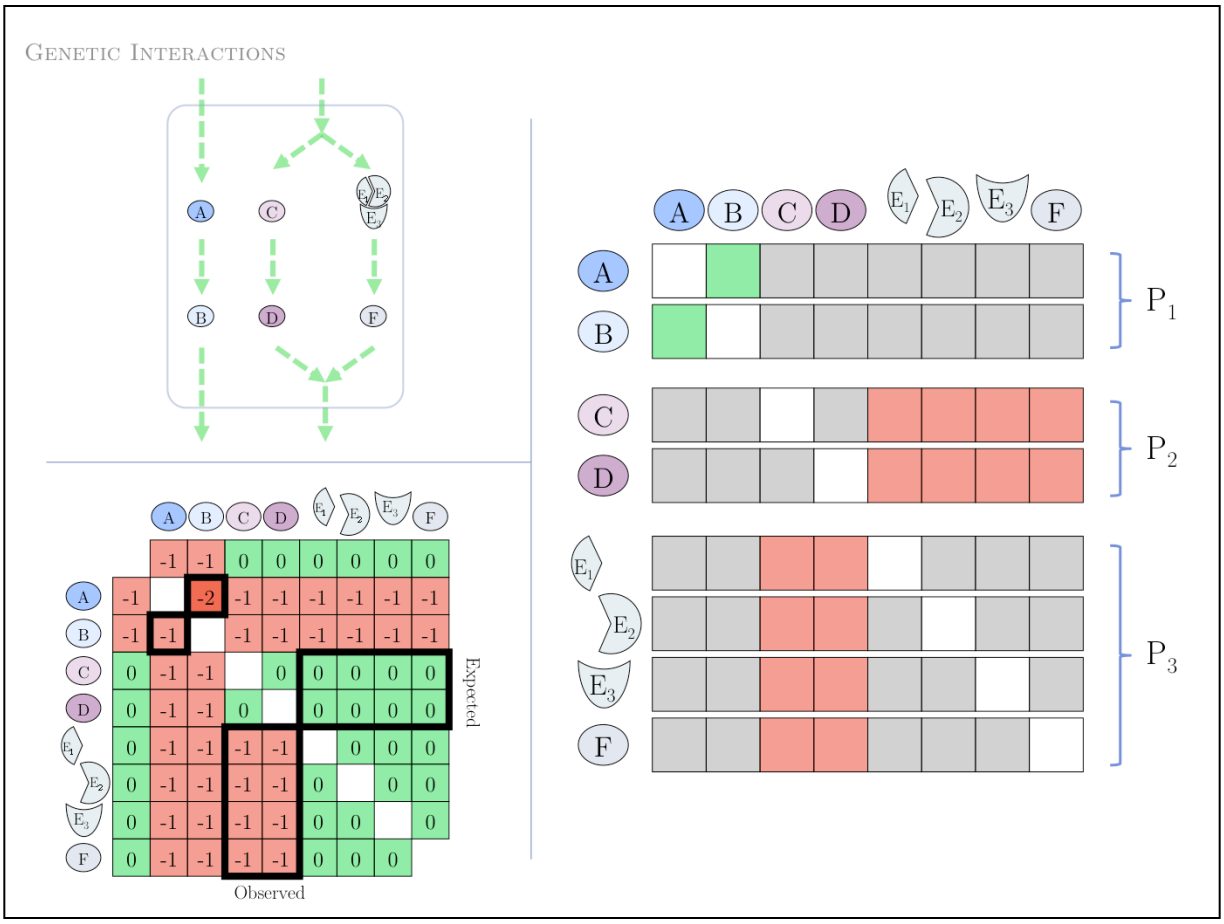


Similarly, any of the simultaneous deletions in both pathways lead to simple additivity. Again, the expected effect and the observed effect are the same and the interactions between the deleted genes are neutral, or nearly so.



Finally, deletions that effect both branches of the right-hand pathway disrupt it. We expect no effect, since none of the individual mutations had an effect, but we obsreve a –1 phenotype (red). These combinations are called “synthetic lethal”, or “synthetic sick”.

Such synthetic effects act through simultaneously interfering with redundant functions.



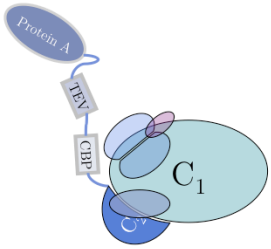
Taken together, the results produce a characteristic vector of effects for each protein, as shown in the rows of the right-hand matrix which is derived from the observations, the lower triangle of the left hand matrix. Positive interactions are green, neutral interactions are grey, and negative interactions are red.

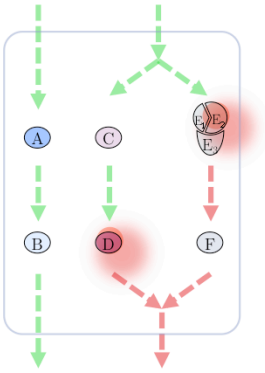
We can now ask: which proteins are similar.

Comparing the rows of the right hand matrix, we easily conclude that A and B fall into one cluster, C and D fall into a second cluster, and E_1, E_2, and E_3, form a third cluster together with F.

This corresponds exactly to the scheme of pathways we started out from.

Genetic "Interactions"





Bottom Line: genetic- and physical interactions carry *complementary information* about biological networks; they can *not* be combined e.g. to calculate confidence scores for interaction data.

(I would prefer using the term *genetic influence* or simply *epistatic effect* ...)

In general: synthetic lethal interactions are for proteins in parallel pathways, they are *not* expected to coincide with physical interactions.

It is unfortunate that we use the same term "interaction" for two incompatible scenarios. You need to be very careful to distinguish between the two.

When in doubt, go with physical inetractions, and don't mix the two.

http://steipe.biochemistry.utoronto.ca/abc

B O R I S . S T E I P E @ U T O R O N T O . C A

DEPARTMENT OF BIOCHEMISTRY & DEPARTMENT OF MOLECULAR GENETICS
UNIVERSITY OF TORONTO, CANADA