

Figure 3.3: **A model of synthetic lethal gene expression.** A conceptual model of synthetic lethal interactions between a Query gene and partner gene (G_X). Genes that are synthetic lethal may not both be non-functional in the same sample without another gene compensating for the loss of function. This is most likely to be detectable as low gene expression, whether they are lost by mutation, deletion, DNA methylation, or suppressing regulatory signals. This could manifest as coexpression, mutual exclusivity, or directional shifts in sample frequency. Thus the alternative hypothesis (H_A) is that synthetic lethal genes will have a reduced frequency of co-loss samples while the null hypothesis (H_0) is that non-synthetic lethal gene pairs would show no such relationship, even if they may be correlated for other means such as pathway relationships. In this model synthetic lethal genes may compensate for the loss of each other but this is not assumed, only that loss of both is unfavourable to cell viability and probability of detecting samples with combined gene loss.

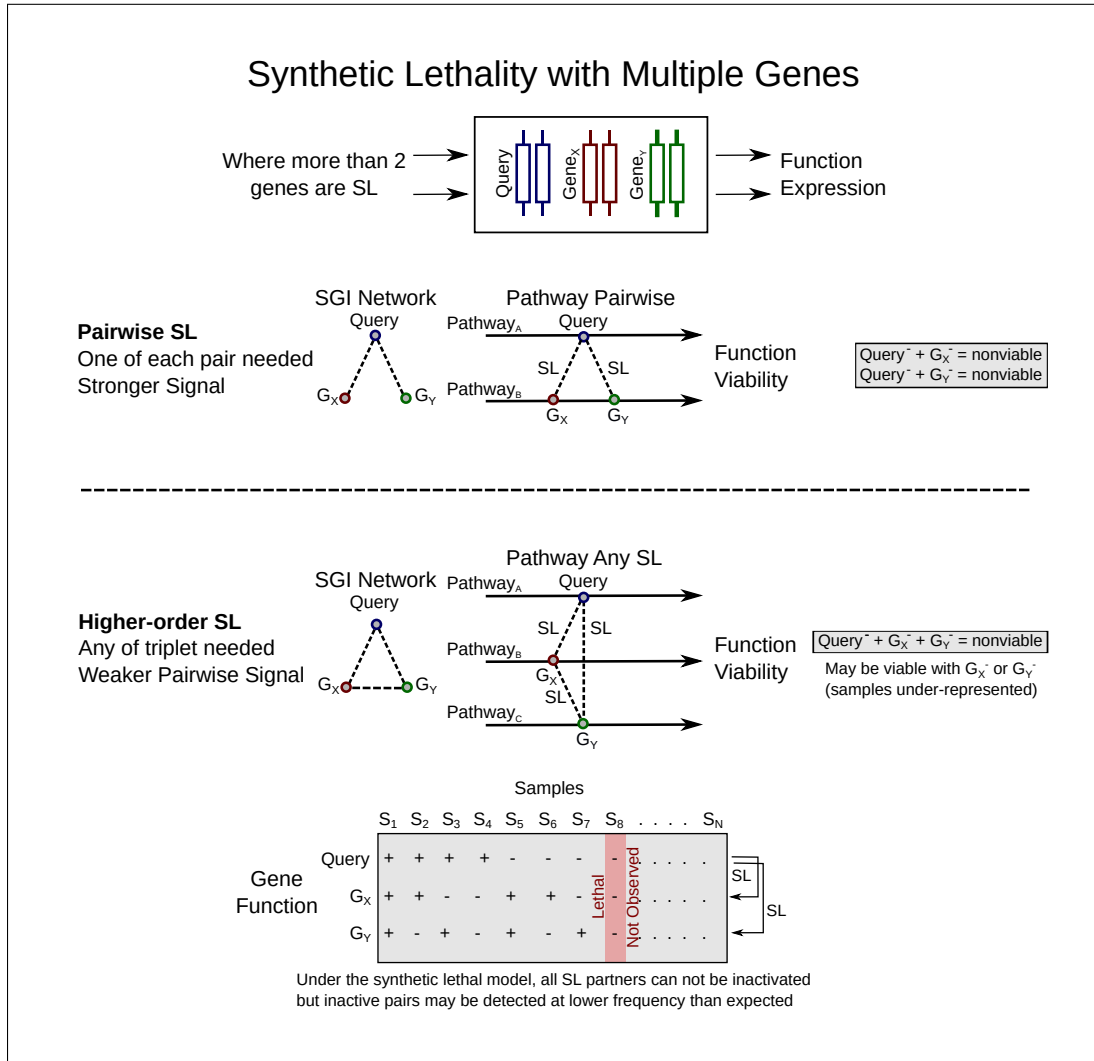


Figure 3.4: **Synthetic lethality with multiple genes.** Higher order synthetic lethal interactions may occur between 3 or more genes, affecting the simulated expression (or synthetic lethal predictions) even if unknown to a pairwise observer. Consider interactions between a Query gene and two partner genes (G_X and G_Y). They may interact with the Query pairwise (inviable when either gene pair is lost) or form a higher-order interaction such as the “synthetic lethal triplet” if any of the genes provide an essential function (inviable only when all are lost). Either is plausible with the potential pathway structures. A synthetic lethal triple has 8 potential combinations of gene functional but one is not expected to be observed (due to inviability) but pairwise inactivation may be observed if additional partner genes are functional. The proportion of these combinations vary depending on the functional threshold.

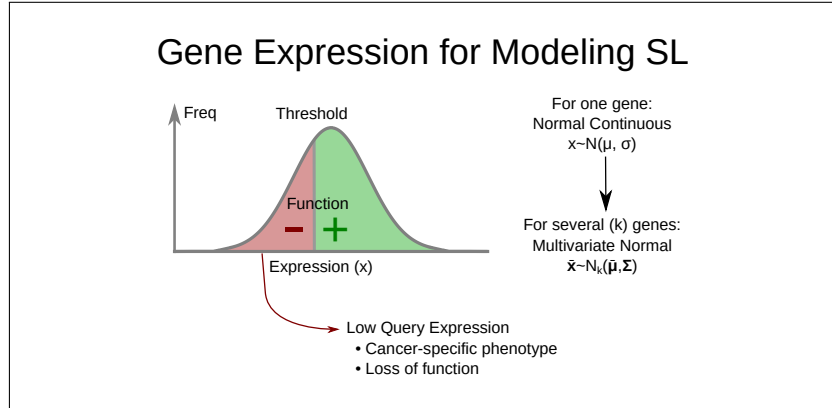


Figure 3.5: **Modeling synthetic lethal gene expression.** When modeling synthetic lethal interactions between a Query gene with partner genes (G_X and G_Y) above, cellular viability requires that at least of genes is not inactivated. Expression below a threshold is used as a model of loss of function, where genes are regarded as non-functional for the purposes of modelling synthetic lethality. Genes with loss of function may also lead to cancer specific phenotypes if they are tumour suppressors (although these thresholds are not necessarily the same). Expression is modeled a normally (Gaussian) distributed continuous data which could be expression data (on a logarithmic scale) from RNA (microarray or RNA-Seq), Protein levels, or pathway metagenes. This rationale generalises for several genes on a multivariate normal distribution.