High-Throughput Sequencing Course

Time Course Hypotheses

Biostatistics and Bioinformatics

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Duke University
School of Medicine

Time-Course Hypothesis

- So far we have considered comparing mean abundance level at a single time-point
- Example: Let μ_0 and μ_1 denote the mean mRNA abundance level for the untreated and treated group
- $H_0 : \mu_0 = \mu_1$ (there is no treatment effect)
- $H_1 : \mu_0 \neq \mu_1$ (there is a treatment effect)
- What may be of interest is to identify genes for which the mRNA abudance level varies over time
- We will consider the one-sample and two-sample time-course hypotheses

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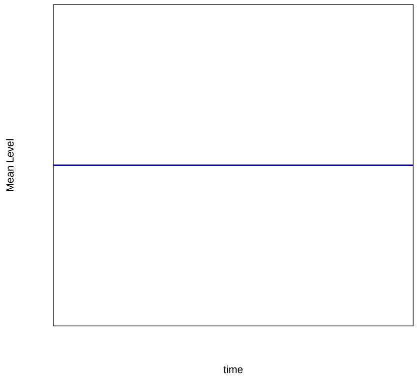
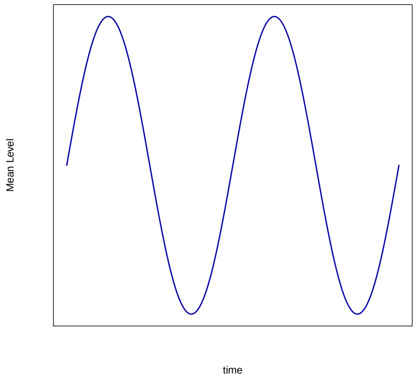
One-Sample Problem: No Time Course Effect

There is no time-course effect: The mean level is constant over time



ONE SAMPLE PROBLEM: TIME COURSE EFFECT

There is a time course effect: The mean level varies over time

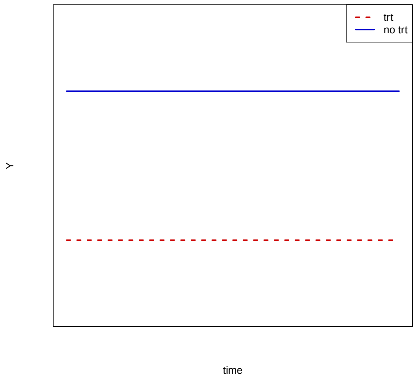


TIME-COURSE HYPOTHESIS: ONE-SAMPLE

- Let $\mu(t)$ denote the mean mRNA abundance level at time $t > 0$
- If the mean level is constant over time, there is no time effect
- $H_0 : \mu(t) = c$ for *all* t for some constant c
- $H_1 : \mu(s) \neq c$ for *some* t

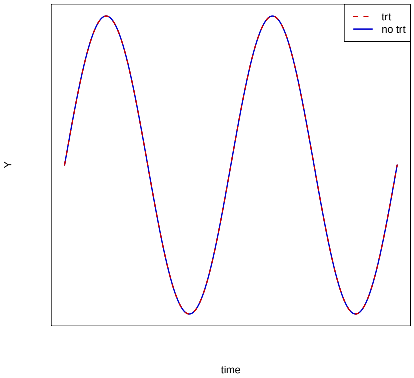
TWO-SAMPLE PROBLEM: TIME COURSE EFFECT?

There is no time-course effect within each condition, while there is a treatment effect. Is this interesting?



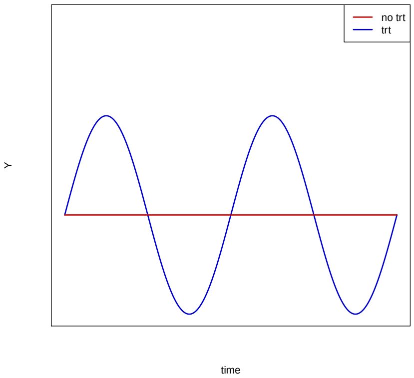
Two-sample Problem: Time Course Effect?

There is a time-course effect within each condition but not time-course effect across conditions. Is this interesting?



Two-sample Problem: Time Course Effect

There is a time-course effect for the treated group only. Is this interesting?

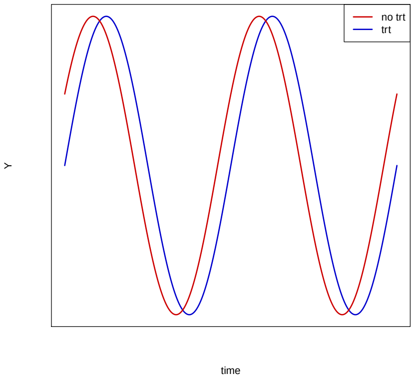


Time-course Hypothesis: Two-Sample

- Let $\mu_0(t)$ denote the mean mRNA abundance level at time $t > 0$ for the *untreated* group
- Let $\mu_1(t)$ denote the mean mRNA abundance level at time $t > 0$ for the *treated* group
- $H_0 : \mu_0(t) = \mu_1(t)$ for *all* t
- $H_0 : \mu_0(t) \neq \mu_1(t)$ for *some* t

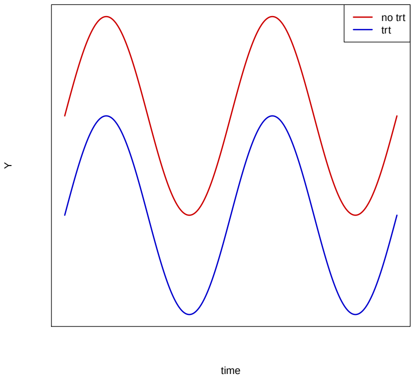
Two-sample Problem: Time Course Effect?

There is a time-course effect within each condition and a phase shift with respect to treatment. Is this interesting?



Two-sample problem: Time Course Effect?

There is a time-course effect within each condition and a vertical shift with respect to treatment. Is this interesting?



Standard Analysis (Not Recommended)

- For each gene, do a two-sample t-test at *each* time point
- Declare a time-course if any of the *P*-values are "significant
- To make things worse: Use the *P*-values to describe the time-course
- This approach ignores multiple testing aspect (not only due to genes but also due to multiple timepoints within each gene)
- This analysis would only be appropriate if one time-point is identified upfront
- What is the point of a time-course experiment if only one timepoint is of interest?

Analysis Methods

- Previously, we have modeled the mean abudance level at a single time point as
$$Y = \mu + \epsilon$$
- You can model the expression level at time t as
$$Y(t) = \mu(t) + \epsilon(t)$$
- The challenge here is that $\mu(t)$ is an unknown function of time
- Methods using this type of model use various approaches for estimating $\mu(t)$