Time Ordering of Gene Co-expression

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Appendix: Auxiliary Results and Proofs

We first list the assumptions needed for the theoretical results. Random trajectories Z_i are supposed to be i.i.d. realizations of a stochastic process Z for which we assume the following properties.

(A1) $E(Z(t)) = 0$ and $\sup_s E(Z(t-s)^2) < \sigma^2 < \infty$, and Z_i is independent of τ_i;

(A2) $\sup_s E \int_{\mathcal{T}} Z(t-s)^2 \,\mathrm{dt} < C_z < \infty$;

(A3) The mean function $\mu(t)$ is a bounded, non-constant, continuous and twice differentiable function with

$$\inf_s \int_{\mathcal{T}} \mu'(t-s)^2 \,\mathrm{dt} > 0, \text{ and } \sup_s \int \mu''(t-s)^2 \,\mathrm{dt} < \infty;$$

(A4) For $G(s) = \int_{\mathcal{T}} \big(\mu(t) - \mu(t-s)\big)^2 \mathrm{dt}$, assume $G(s) \neq G(s')$, if $s \neq s'$;

(A5) The trajectories of Z are continuous and twice differentiable on $\mathcal{T}$;

(A6) $\sup_s E \left(\int_{\mathcal{T}} \big(Z''(t-s)\big)^2 \,\mathrm{dt} \right) < \infty$.

The measurements are assumed to satisfy $Y_{im} = X_i(t_{im}, \tau_i) + e_{im}$, for a fixed and dense grid of n measurements, $t_{i1} \leq t_{i2} \leq \ldots \leq t_{in}$, such that $\sup_{1 \leq i \leq K, 1 \leq m \leq n-1} \big| t_{im+1} - t_{im} \big| = O(n^{-1})$, and for i.i.d. errors e_{im} with $E(e_{im}) = 0$ and $\mathrm{var}(e_{im}) = \sigma_e^2 < \infty$. The $\tilde{s}_{ij}$ (3.3) are based on smoothed versions $\hat{X}_i$ of the processes X_i. A kernel smoothing method can be used for this purpose. Assume h is a sequence of positive bandwidths such that $h \to 0, nh \to \infty$ as $n \to \infty$, and let W be a bounded kernel function on a compact support satisfying $\int W(x)dx = 1$ and $\int W(x)^2 dx < \infty$. Then a possible estimate can be obtained as follows (Gasser and Müller, 1984):

$$\hat{X}_i(t) = \frac{1}{h}\sum_{j=1}^{n} Y_{im} \int_{v_{im-1}}^{v_{im}} W(\frac{t-u}{h})\,\mathrm{du}, \tag{A-1}$$

where $0 = v_{i0} \leq v_{i1} \leq \ldots \leq v_{in} = T$, $v_{im} = \dfrac{t_{im} + t_{im+1}}{2}, m = 1, \ldots, n-1, 1 \leq i \leq K$.

Lemma 1. *Assume the twice continuously differentiable function H satisfies $H'(s_0) = 0$, $H''(s_0) > 0$, and $H(s_0) < H(s)$ for all $s \neq s_0$, and a function H_ε satisfies*

$$\sup_s |H_\varepsilon(s) - H(s)| \leq \varepsilon. \tag{A-2}$$

Then $\check{s} = \arg\min_s H_\varepsilon(s)$ satisfies

$$|\check{s} - s_0| = O(\varepsilon^{\frac{1}{2}}), \quad \textit{as} \quad \varepsilon \to 0.$$

Proof. By (A-2), we have $-\varepsilon \leq H_\varepsilon(s) - H(s) \leq \varepsilon$, for all s. Let $\tilde{H}_\varepsilon(s) = H_\varepsilon(s) + 2\varepsilon$, then $\check{s} = \arg\min_s \tilde{H}_\varepsilon(s)$, and $\varepsilon \leq \tilde{H}_\varepsilon(s) - H(s) \leq 3\varepsilon$, for all s. Let η be s.t. $\eta \geq |\check{s} - s_0|$, and $H(s_0 + \eta) = \tilde{H}_\varepsilon(\check{s})$, assuming $\check{s} > s_0$, w.l.o.g. By Taylor expansion, $H(s_0 + \eta) = H(s_0) + \eta^2 H''(s_0)/2 + o(\eta^2)$, since $H'(s_0) = 0$ and it follows that $\eta^2 H''(s_0)/2 \leq 3\varepsilon + o(\eta^2)$. Since $H''(s_0) > 0$, we have $\eta^2 \leq C\varepsilon$, for a suitable $C > 0$, so that $|\eta| < C'\varepsilon^{\frac{1}{2}}$, and therefore, $|\check{s} - s_0| = O(\varepsilon^{\frac{1}{2}})$.

Proof of Theorem 1. Since at $s = 0$, $(d/ds)G(s) = 0$, G has a local extremum at $s = 0$ by (A3) and (A4). For the second derivative of G at $s = 0$, $(d^2/d^2s)G(s) > 0$ by (A3). Therefore G has a local minimum at $s = 0$ with $G(0) = 0$, $G'(0) = 0$, and $G''(0) > 0$. Let $H_{ij}(s) = \int_{\mathcal{T}} \left(\mu(t - \tau_i) - \mu(t - \tau_j - s)\right)^2 \mathrm{dt}$, then $(d/ds)H_{ij}(s) = 0$ at

$s = \tau_i - \tau_j$. Hence, each H_{ij} has a local extremum at $s = s^*_{ij} = \tau_i - \tau_j$ by (A3) and (A4). For the second derivative of H_{ij} at $s = \tau_i - \tau_j$, $(d^2/d^2s)H_{ij}(s) = 2\int \mu'(t-\tau_i)^2\,\mathrm{dt} > 0$, by (A3). Therefore, $H_{ij}(s)$ has a local minimum at $s = \tau_i - \tau_j$ with $H_{ij}(\tau_i - \tau_j) = 0$, $H'_{ij}(\tau_i - \tau_j) = 0$, $H''_{ij}(\tau_i - \tau_j) > 0$, and

$$
\begin{aligned}
& \sup_s |\Delta_{ij}(s) - H_{ij}(s)| \\
= \; & \sup_s \left| E\left(\int_{\mathcal{T}} \left(X_i(t,\tau_i) - X_j(t-s,\tau_j)\right)^2 \mathrm{dt} \,\Big|\, \tau_i,\tau_j \right) - \int_{\mathcal{T}} \left(\mu(t-\tau_i) - \mu(t-\tau_j-s)\right)^2 \mathrm{dt} \right| \\
\leq \; & \sup_s \left| \delta^2 E\left(\int_{\mathcal{T}} \left(Z_i(t-\tau_i) - Z_j(t-\tau_j-s)\right)^2 \mathrm{dt} \,\Big|\, \tau_i,\tau_j \right) \right| \\
& + \sup_s \left| 2\delta E\left(\int_{\mathcal{T}} \left(\mu(t-\tau_i) - \mu(t-\tau_j-s)\right)\left(Z_i(t-\tau_i) - Z_j(t-\tau_j-s)\right) \mathrm{dt} \,\Big|\, \tau_i,\tau_j \right) \right| \\
= \; & I + II.
\end{aligned}
$$

Next observe

$$
\begin{aligned}
I \; \leq \; & \sup_s \left| \delta^2 E\left(\int_{\mathcal{T}} \left(Z_i(t-\tau_i)\right)^2 \mathrm{dt} \,\Big|\, \tau_i,\tau_j \right) \right| + \sup_s \left| \delta^2 E\left(\int_{\mathcal{T}} \left(Z_j(t-\tau_j-s)\right)^2 \mathrm{dt} \,\Big|\, \tau_i,\tau_j \right) \right| \\
& + \sup_s \left| 2\delta^2 E\left(\int_{\mathcal{T}} Z_i(t-\tau_i) Z_j(t-\tau_j-s)\, \mathrm{dt} \,\Big|\, \tau_i,\tau_j \right) \right| \\
\leq \; & 2\delta^2 C < \infty,
\end{aligned}
$$

for $1 \leq i, j \leq K$ by (A1) and (A2), since Z_i and Z_j are independent. By (A1),

$$
II = \sup_s \left| 2\delta \int_{\mathcal{T}} \left[\left(\mu(t-\tau_i) - \mu(t-\tau_j-s)\right) E\left(Z_i(t-\tau_i) - Z_j(t-\tau_j-s) \,|\, \tau_i,\tau_j\right) \right] \mathrm{dt} \right| = 0.
$$

Therefore, $\sup_s |\Delta_{ij}(s) - H_{ij}(s)| \leq 2\delta^2 C = O(\delta^2)$, and by Lemma 1, $s_{ij} = \arg\min_s \Delta_{ij}(s) = s^*_{ij} + O(\delta) = \tau_i - \tau_j + O(\delta)$.

Lemma 2. *Assume the design points t_{im} are equidistant on $[0,T]$. Under assumptions (A-1) on the kernel function, choosing $h \sim n^{-\frac{1}{5}}$ as $n \to \infty$ and assuming (A1), (A3), (A5), and (A6) and*

$$\left|\max_{i,m} |v_{im} - v_{im-1}| - \frac{1}{n}\right| = O(n^{-\delta}),\ \delta > 1,$$

it holds that

$$\sup_{1\le i\le K} \sup_s E\left(\int (\hat{X}_i(t-s,\tau_i) - X_i(t-s,\tau_i))^2 \,\mathrm{dt} \,\Big|\, \tau_i \right) = O_p(n^{-\frac{4}{5}}). \tag{A-3}$$

Proof. Applying results from Gasser and Müller (1984), let $B = \int W(x)x^2 \,\mathrm{dx} < \infty$, $V = \int W(x)^2 \,\mathrm{dx} < \infty$, $B \neq 0$ and $V \neq 0$, then the supremum of the conditional integrated squared bias of $\hat{X}_i(t,\tau_i)$ is

$$\begin{aligned} & \sup_s \int \left\{ E\left[\hat{X}_i(t-s,\tau_i) - X_i(t-s,\tau_i) \,\Big|\, \tau_i \right] \right\}^2 \mathrm{dt} \\ = & \sup_s \left\{ h^4 \left[\frac{B}{2} \int \left[\mu''(t-\tau_i-s) + \delta^2 E\big(Z_i''(t-\tau_i-s) \,\big|\, \tau_i\big) \right] \mathrm{dt} \right]^2 + o(1) + O(n^{-1}) \right\} \\ = & O_p(h^4), \end{aligned}$$

by (A3), (A6) and the Cauchy-Schwarz inequality. The integrated variance of $\hat{X}_i(t,\tau_i)$ is

$$\int \mathrm{var}\Big(\hat{X}_i(t-s,\tau_i) \,\Big|\, \tau_i \Big) \,\mathrm{dt} = \frac{1}{nh}\left[\sigma^2 V + O(1)\right] = O(\frac{1}{nh}).$$

The mean integrated square error (MISE) of $\hat{X}_i(t,\tau_i)$ is then

$$\sup_s E\left(\int \big(\hat{X}_i(t-s,\tau_i) - X_i(t-s,\tau_i)\big)^2 \,\mathrm{dt} \,\Big|\, \tau_i \right) = O_p(\frac{1}{nh} + h^4).$$

The conditional MISE at optimal global bandwidth, $h \sim n^{-\frac{1}{5}}$ is then $O_p(n^{-\frac{4}{5}})$. Since K is finite, (A-3) follows.

Lemma 3. *Define*

$$\tilde{\Delta}_{ij}(s) = E\left(\int_{\mathcal{T}} (\hat{X}_i(t,\tau_i) - \hat{X}_j(t-s,\tau_j))^2 \,\mathrm{dt} \,\Big|\, \tau_i, \tau_j \right).$$

Under conditions of (A1) - (A6), for all $0 \le \tau_i, \tau_j < T$,

$$\sup_s |\Delta_{ij}(s) - \tilde{\Delta}_{ij}(s)| = O_p(n^{-\frac{2}{5}}).$$

Proof. Note

$$\begin{aligned}
& \sup_s |\Delta_{ij}(s) - \tilde{\Delta}_{ij}(s)| \\
\le\ & \sup_s \left| E\left(\int_{\mathcal{T}} \left(\hat{X}_i^2(t,\tau_i) - X_i^2(t,\tau_i)\right) \mathrm{dt} \,\Big|\, \tau_i \right) \right| \\
& + \sup_s \left| E\left(\int_{\mathcal{T}} \left(\hat{X}_j^2(t-s,\tau_j) - X_j^2(t-s,\tau_j)\right) \mathrm{dt} \,\Big|\, \tau_j \right) \right| \\
& + \sup_s \left| 2E\left(\int_{\mathcal{T}} \left(\hat{X}_i(t,\tau_i)\hat{X}_j(t-s,\tau_j) - X_i(t,\tau_i)X_j(t-s,\tau_j)\right) \mathrm{dt} \,\Big|\, \tau_i, \tau_j \right) \right| \\
=\ & I + II + III,
\end{aligned}$$

$$\begin{aligned}
I \ \le\ & \sup_s E\left(\int_{\mathcal{T}} |\hat{X}_i(t,\tau_i) - X_i(t,\tau_i)||\hat{X}_i(t,\tau_i) + X_i(t,\tau_i)| \,\mathrm{dt} \,\Big|\, \tau_i \right) \\
\le\ & \sup_s E\left(\int_{\mathcal{T}} \left(\hat{X}_i(t,\tau_i) - X_i(t,\tau_i)\right)^2 \mathrm{dt} \,\Big|\, \tau_i \right) \\
& + \sup_s E\left(2\int_{\mathcal{T}} |\hat{X}_i(t,\tau_i) - X_i(t,\tau_i)||X_i(t,\tau_i)| \,\mathrm{dt} \,\Big|\, \tau_i \right) = O_p(n^{-\frac{2}{5}}),
\end{aligned}$$

using the Cauchy-Schwarz inequality, (A1) - (A3) and lemma 2. Analogously, $II = O_p(n^{-\frac{2}{5}})$, and furthermore,

$$\begin{aligned}
III \ \le\ & \sup_s \left| 2E\left(\int_{\mathcal{T}} \left(\hat{X}_i(t,\tau_i) - X_i(t,\tau_i)\right) X_j(t-s,\tau_j) \,\mathrm{dt} \,\Big|\, \tau_i, \tau_j \right) \right| \\
& + \sup_s \left| 2E\left(\int_{\mathcal{T}} \left(\hat{X}_j(t-s,\tau_j) - X_j(t-s,\tau_j)\right)\left(\hat{X}_i(t,\tau_i) - X_i(t,\tau_i)\right) \mathrm{dt} \,\Big|\, \tau_i, \tau_j \right) \right| \\
& + \sup_s \left| 2E\left(\int_{\mathcal{T}} \left(\hat{X}_j(t-s,\tau_j) - X_j(t-s,\tau_j)\right) X_i(t,\tau_i) \,\mathrm{dt} \,\Big|\, \tau_i, \tau_j \right) \right|
\end{aligned}$$

$$
\begin{aligned}
\le\ & \sup_s \left\{ 2E\left(\int_{\mathcal{T}} \left(\hat{X}_i(t,\tau_i) - X_i(t,\tau_i)\right)^2 \mathrm{dt} \,\Big|\, \tau_i \right)^{\frac{1}{2}} E\left(\int_{\mathcal{T}} X_j(t-s,\tau_j)^2 \,\mathrm{dt} \ \Big|\, \tau_j \right)^{\frac{1}{2}} \right\} \\
& + \sup_s \left\{ 2E\left(\int_{\mathcal{T}} \left(\hat{X}_j(t-s,\tau_j) - X_j(t-s,\tau_j)\right)^2 \mathrm{dt} \,\Big|\, \tau_j \right)^{\frac{1}{2}} \right. \\
& \left. \times E\left(\int_{\mathcal{T}} \left(\hat{X}_i(t,\tau_i) - X_i(t,\tau_i)\right)^2 \mathrm{dt} \ \Big|\, \tau_i \right)^{\frac{1}{2}} \right\} \\
& + \sup_s \left\{ 2E\left(\int_{\mathcal{T}} \left(\hat{X}_j(t-s,\tau_j) - X_j(t-s,\tau_j)\right)^2 \mathrm{dt} \,\Big|\, \tau_j \right)^{\frac{1}{2}} E\left(\int_{\mathcal{T}} X_i(t,\tau_i)^2 \,\mathrm{dt} \ \Big|\, \tau_i \right)^{\frac{1}{2}} \right\} \\
=\ & O_p(n^{-\frac{2}{5}})
\end{aligned}
$$

by (A1)-(A3), Lemma 2, and the Cauchy-Schwarz inequality. This implies the result.

Proof of Theorem 2. Note $\sup_s |H_{ij}(s) - \tilde{\Delta}_{ij}(s)| \le \sup_s |H_{ij}(s) - \Delta_{ij}(s)| + \sup_s |\Delta_{ij}(s) - \tilde{\Delta}_{ij}(s)| = O(\delta^2) + O(n^{-\frac{2}{5}})$, using Theorem 1 and Lemma 3. By Lemma 1, $\tilde{s}_{ij} = \arg\min_s \tilde{\Delta}_{ij}(s) = \tau_i - \tau_j + O(\delta) + O_p(n^{-\frac{1}{5}})$.

Proof of Corollary 1. From equation (3.5), $\hat{\tau} = (A'A)^{-1}A'\tilde{s} = (A'A)^{-1}A'(s + O(\delta) + O_p\big(n^{-\frac{1}{5}})\big) = \tau + O(\delta) + O_p(n^{-\frac{1}{5}})$, where we observe that $\det(A'A) > 0$.