Supplementary material.

Multi-Scale Tissue Architecture Analysis

A Region of Interest (ROI) is drawn by a cytotechnologist on the Feulgen-thionin-stained image under a pathologist’s supervision (Fig. 1). Glands contour were drawn by two experienced cytotechnicians. Special attention was done to respect the integrity of the basal membrane of each acinus. We are developing an algorithm to automatically detect these structures but this is not the focus of this study.

Let $x_i$ and $y_i$ be the coordinates of the $i^{th}$ nuclei in the ROI. For simplicity, even though this tessellation is based on the center of gravity of the nuclei, we will use the term cell instead of nuclei. Let $n_N$ be the number of cells in the ROI. Let $ROI_{Area}$ be the area of the ROI (in microns).

1. Nuclei-based Tissue Architecture (NbTA)

   Let $n_{VD}$ be the Voronoi Diagram generated from the $n^{th}$ nuclei in the ROI. Let $V_i$ be the $i^{th}$ Voronoi polygon associated with the $i^{th}$ cell. ROI_{Area} is the area of the ROI in microns.

   Each seed (nucleus) whose associated Voronoi polygon intersects with the ROI, is considered marginal and is excluded from the calculation of some of the architectural features (Fig. 1). Let $n$ be the total number of nuclei and $n_{nm}$ is the number of non-marginal nuclei.

   **a. Cell density**

   \[
   \text{Cell Density} = \frac{n}{ROI_{Area}}
   \]

   **b. Voronoi diagram-derived features**

   - **Area**

     Let $A_i$ be the area of the $i^{th}$ Voronoi polygon. We calculate $n_{VorArea1}$ and $n_{VorArea2}$, which is respectively, the mean and standard deviation of the distribution of the $n_{nm} A_i$ values.

   - **Perimeter**

     Let $P_i$ be the perimeter of the $i^{th}$ Voronoi polygon. We calculate $n_{VorPeri1}$ and $n_{VorPeri2}$ which is respectively, the mean and standard deviation of the distribution of the $n_{nm} P_i$ values.

   - **Roundness Factor**

     Let $RF_i$ be the Roundness Factor of the $i^{th}$ Voronoi polygon.

     \[
     RF_i = \frac{(4\pi A_i)^{1/2}}{P_i}
     \]

     We calculate $n_{VorRF1}$ and $n_{VorRF2}$ which is respectively, the mean and standard deviation of the distribution of the $n_{nm} RF_i$ values.

   - **Entropy**

     Entropy, $n_{Entro}$, is a measure of the disorder in the ROI.

     \[
     n_{Entro} = \log(n_{nm}) - \sum \left(\frac{H_i}{\log(1/ H_i)}\right) \text{ where } H_i = \frac{A_i}{ROI_{Area}}
     \]

   **c. Delaunay graph-derived features**

   Delaunay graph is the dual graph of the Voronoi diagram. Two nuclei are called Delaunay neighbors if they share a common Voronoi edge.

   - **Number of Delaunay neighbors ($n_{NbDN}$)**

     Let $NbDN_i$ be the number of Delaunay Neighbors of the $i^{th}$ nucleus. Let $n_{NbDN1}$ and $n_{NbDN2}$ be respectively, the mean and standard deviation of all $n_{nm} n_{NbDN}$ values.
- Averaged Distance to the Delaunay Neighbors (nADDN)
Let \( nADDN_i \) be the average distance of the \( i^{th} \) nucleus to its \( k \) Delaunay neighbors. Let \( nADDN_1 \) and \( nADDN_2 \) be respectively, the mean and standard deviation of all \( n \) \( nADDN \) values.

- Average Distance to the Three Nearest Delaunay Neighbors (nADTN)
Let \( nADTN_DNi \) be the average distance of the \( i^{th} \) nucleus to its three nearest Delaunay neighbors. Let \( nADTN_DN_1 \) and \( nADTN_DN_2 \) be respectively, the mean and standard deviation of all \( n \) \( nADTN_DN \) values.

- Distance to the Nearest Delaunay Neighbor (nDN)
Let \( nDN_DNi \) be the distance of the \( i^{th} \) nucleus to its nearest Delaunay neighbor. Let \( nDN_1 \) and \( nDN_2 \) be respectively, the mean and standard deviation of all \( n \) \( nDN \) values.

d. Minimum Spanning Tree-derived features
A minimum spanning tree (MST) is the subset of the edges of the Delaunay graph that connects all the vertices together without any cycles and with the minimum possible total length.
Let \( d_i \) be the length of the \( i^{th} \) edge of the cMST. Let \( cMST_1 \) and \( cMST_2 \) be respectively, the mean and the standard deviation of the distribution of the \( N - 1 \) edge values of the cMST.

2. Gland-based Tissue Architecture (GbTA)
The center of gravity of each gland is used as a seed (vertex) of the Gland-based Voronoi diagram (gVD). Let \( g \) be the number of glands in the ROI and let \( Vgi \) be the Voronoi polygon associated with the \( i^{th} \) gland (\( i = 1 \) to \( N_g \)). Each seed (gland) whose associated Voronoi polygon intersects the ROI, is called marginal and is excluded from the calculation of some of the architectural features (Fig. 1). Let \( g \) be the total number of glands and \( gnm \) is the number of non-marginal glands.

a. Glands density
\[
GlandDens = g / \text{ROI\_area}.
\]

b. Voronoi diagram-derived features
- Area
Let \( Ai \) be the area of the \( i^{th} \) Voronoi polygon. We calculate \( gVorArea_1 \) and \( gVorArea_2 \) which is respectively, the mean and standard deviation of the distribution of the \( gnm \) \( Ai \) values.
- Perimeter
Let \( Pi \) be the perimeter of the \( i^{th} \) Voronoi polygon. We calculate \( gVorPeri_1 \) and \( gVorPeri_2 \) which is respectively, the mean and standard deviation of the distribution of the \( gnm \) \( Pi \) values.
- Roundness Factor
Let \( RFi \) be the Roundness factor of the \( i^{th} \) Voronoi polygon.
\[
RFi = \frac{(4\pi \times Ai)}{(P_i \times P_i)}
\]
We calculate \( gVorRF_1 \) and \( gVorRF_2 \) which is respectively, the mean and the standard deviation of the distribution of all \( gnm \) \( RFi \) values.
- Entropy
Entropy, \( gEntro \), is a measure of the disorder in the ROI.
\[
gEntro = \log(gnm) - \sum(H_i / \log(1/ H_i)) \quad \text{where} \quad H_i = Ai / (\text{ROI\_Area})
\]

c. Delaunay graph-derived features
Delaunay graph is the dual graph of the Voronoi diagram. Two glands are called Delaunay neighbors if they share a common Voronoi edge.

- Number of Delaunay neighbors (gNbDN)
Let \( NbDN_i \) be the number of Delaunay neighbors of the \( i^{th} \) gland. Let \( gNbDN_1 \) and \( gNbDN_2 \) be respectively, the mean and
standard deviation of all $g_n m$ $g^{nb}D_{N}$ values.

- **Average Distance to the Delaunay Neighbors (gADDN)**
  For each gland, let $g^{DD}_{N}$ be the average distance to its $k$ Delaunay neighbors. Let $g^{ADD}_{N1}$ and $g^{ADD}_{N2}$ be respectively, the mean and standard deviation of all $g_n m$ $g^{ADD}_{N}$ values.

- **Average Distance to the Three Nearest Delaunay Neighbors (gADTNDN)**
  For the $i^{th}$ gland, $g^{ADTND}_{Ni}$ be the average distance to its Three nearest Delaunay neighbors. Let $g^{ADTND}_{N1}$ and $g^{ADTND}_{N2}$ be respectively, the average and standard deviation of all $g_n m$ $g^{ADTND}_{N}$ values.

- **Distance to the Nearest Delaunay Neighbor (gDNDN)**
  Let $g^{DND}_{Ni}$ be the distance of the $i^{th}$ gland to its nearest Delaunay neighbor. Let $g^{DND}_{N1}$ and $g^{DND}_{N2}$ be respectively, the mean and standard deviation of all $g^{DND}_{N}$ values.

**d. Minimum Spanning Tree-derived features**

Let $d_i$ be the length of the $i^{th}$ edge of the gMST. Let $g^{MST}_{1}$ and $g^{MST}_{2}$ be respectively, the mean and standard deviation of the distribution of the $N - 1$ edge values of the gMST.

**3. Glands Phenotype (GlandPheno)**

**a. Gland Morphology**

Three morphological features were calculated for each gland: the size, $gl^{Area}$; the perimeter, $gl^{Peri}$; and the Roundness Factor, $gl^{RF}$.

Let $gl^{Area1}$ and $gl^{Area2}$ be respectively, the mean and standard deviation of the area values of the $g$ glands.

Let $gl^{Peri1}$ and $gl^{Peri2}$ be respectively, the average and standard deviation of the Perimeter for all glands of the ROI.

Let $gl^{RF1}$ and $gl^{RF2}$ be respectively, the average and standard deviation of the area for all glands of the ROI.

**b. Gland Architecture**

A Voronoi diagram is constructed based on the nuclei positions *within* each gland.

For each gland, we calculate the same architectural features described previously for the NbTA analysis.

For each ROI, the mean and standard deviation of each architectural feature of the $n$ glands are calculated as follows:

- $Gl^{Den1}$, $Gl^{Den2}$ : mean and standard deviation of the cellular density of all glands
- $Gl^{Entropy1}$, $Gl^{Entropy2}$ : mean and standard deviation of the entropy of all glands
- $Mean_{gl}^{VorArea1}$ and $Stdv_{gl}^{VorArea1}$, mean and standard deviation of the $gl^{VorArea1}$
- $Mean_{gl}^{VorArea2}$ and $Stdv_{gl}^{VorArea2}$, mean and standard deviation of the $gl^{VorArea2}$
- $Mean_{gl}^{VorPeri1}$ and $Stdv_{gl}^{VorPeri1}$, mean and standard deviation of the $gl^{VorPeri1}$
- $Mean_{gl}^{VorPeri2}$ and $Stdv_{gl}^{VorPeri2}$, mean and standard deviation of the $gl^{VorPeri2}$
- $Mean_{gl}^{VorRF1}$ and $Stdv_{gl}^{VorRF1}$, mean and standard deviation of the $gl^{VorRF1}$
- $Mean_{gl}^{VorRF2}$ and $Stdv_{gl}^{VorRF2}$, mean and standard deviation of the $gl^{VorRF2}$
- $Mean_{gl}^{NbDN1}$ and $Stdv_{gl}^{NbDN1}$, mean and standard deviation of the $gl^{NbDN1}$
- $Mean_{gl}^{NbDN2}$ and $Stdv_{gl}^{NbDN2}$, mean and standard deviation of the $gl^{NbDN2}$
- $Mean_{gl}^{ADDN1}$ and $Stdv_{gl}^{ADDN1}$, mean and standard deviation of the $gl^{ADDN1}$
- $Mean_{gl}^{ADDN2}$ and $Stdv_{gl}^{ADDN2}$, mean and standard deviation of the $gl^{ADDN2}$
- $Mean_{gl}^{ADTNDN1}$ and $Stdv_{gl}^{ADTNDN1}$, mean and standard deviation of the $gl^{ADTNDN1}$
- $Mean_{gl}^{ADTNDN2}$ and $Stdv_{gl}^{ADTNDN2}$, mean and standard deviation of the $gl^{ADTNDN2}$
- $Mean_{gl}^{DNDN1}$ and $Stdv_{gl}^{DNDN1}$, mean and standard deviation of the $gl^{DNDN1}$
- $Mean_{gl}^{DNDN2}$ and $Stdv_{gl}^{DNDN2}$, mean and standard deviation of the $gl^{DNDN2}$
- $Mean_{gl}^{MST1}$ and $Stdv_{gl}^{MST1}$, mean and standard deviation of the $gl^{MST1}$
- $Mean_{gl}^{MST2}$ and $Stdv_{gl}^{MST2}$, mean and standard deviation of the $gl^{MST2}$
Supplementary Fig. 1. A Voronoi diagram generated by the centers of gravity of nuclei (following segmentation). Black line denotes the Region of Interest. Green dots are centers of nuclei. Red polygons are Voronoi polygons associated with each nucleus. White polygons are marginal polygons, i.e. Voronoi polygons that intersect with the edge of the ROI. Green circles correspond to nuclei that are Delaunay neighbors of the nucleus identified by a big red circle, i.e. they share a common Voronoi boundary.