Appendix

Improved vesselness filter

The Frangi vesselness filter uses local structure information in the image to identify tubular shape of vessels. The detail of this method was previously described.(18) In summary, the local structure of every pixel in the image was represented by the eigenvalues (λ_1 and λ_2) and eigenvectors ($\vec{\vartheta}_1$ and $\vec{\vartheta}_2$) decomposed from the two-dimensional Hessian matrix of the image. This eigendecomposition is performed at multiple Gaussian scale level by applying different sizes of convolutional kernel to the image therefore ensuring the identification of a range of sizes of local structure. At every pixel and scale level, the probability-like estimates of the vessel, or Frangi response, is calculated using two criteria of eigenvalues combination,

$$F = e^{-\frac{S_1}{\beta_1}} \cdot \left(1 - e^{-\frac{S_2}{\beta_2}}\right)$$

$$S_1 = \left(\frac{\lambda_1}{\lambda_2}\right)^2$$

$$S_2 = {\lambda_1}^2 + {\lambda_2}^2$$

where F is the Frangi response, S_1 and S_2 are the factors that determines the geometrical shape of the local structure, and β_1 and β_2 are the correction constants. The final Frangi response of a pixel is the highest response at that pixel among the scale space.

In our application, the convolutional kernel is a two-dimensional array of $(6\sigma + 1)$ by $(6\sigma + 1)$ pixels, with σ representing the variance of the Gaussian filter. We used σ value ranging from 2 to 7 which yielded accurate visualization of the vessels with diameter 5 to 15 pixels. We found that the correction constants 0.5 and 15 provided better vessel enhancement.

However, the multiscale approach was prone to the false enhancement of the pixels surrounding the vessel in proportion to the scale level in which the final Frangi response for that pixel was selected. To overcome this so-called blur problem, we introduced a third factor to the Frangi response equation.

$$S_3 = \frac{I - I_{min}}{I_{max} - I_{min}}$$

where I is the target pixel intensity and I_{max} and I_{min} are the maximum and the minimum pixel intensity, respectively, among the neighboring pixels including the target pixel. With this factor, the high Frangi response of the pixels close to a vessel was reduced since the intensity of these pixels were relatively low compared to the intensity of the vessel. The differences between the result of vesselness filter without and with the normalization factor is shown in Figure 4 in the online-only Data Supplement.