Appendix eI: Derivation of the equations for V_{4DCT}^{HU} and V_{4DCT}^{Jac}

Simon [1] derived a relationship between the regional change in fractional air content and regional volume change, which was adapted to the relationship between the local Hounsfield unit (HU) change and local volume change by Guerrero *et al.* [2]. The specific ventilation in the voxel at location (x, y, z) is given by

$$\frac{\Delta \mathrm{Vol}}{\mathrm{Vol}_{\mathrm{ex}}^{\mathrm{air}}(x,y,z)} = 1000 \frac{\mathrm{HU}_{\mathrm{in}}\{x+u_x(x,y,z), y+u_y(x,y,z), z+u_z(x,y,z)\} - \mathrm{HU}_{\mathrm{ex}}(x,y,z)}{\mathrm{HU}_{\mathrm{ex}}(x,y,z)\left[\mathrm{HU}_{\mathrm{in}}\{x+u_x(x,y,z), y+u_y(x,y,z), z+u_z(x,y,z)\}+1000\right]}, \quad (1)$$

where HU is the HU value and u is the displacement vector mapping the voxel at location (x, y, z) of a peak-exhale 4D-CT image to the corresponding location of a peak-inhale image. Note that the air and tissue densities were assumed to be -1000 and 0 HU, respectively. The peak-exhale air volume ($\mathrm{Vol}_{\mathrm{ex}}^{\mathrm{air}}$) in the voxel at location (x, y, z) can be estimated by

$$\mathrm{Vol}_{\mathrm{ex}}^{\mathrm{air}}(x,y,z) = -\frac{\mathrm{HU}_{\mathrm{ex}}(x,y,z)}{1000}\mathrm{Vol}_{\mathrm{ex}}^{\mathrm{voxel}}(x,y,z), \quad (2)$$

where $\mathrm{Vol}_{\mathrm{ex}}^{\mathrm{voxel}}$ is the exhale voxel volume [3]. Substitution of Equation (2) into Equation (1) yields

$$\Delta \mathrm{Vol} = \frac{\mathrm{HU}_{\mathrm{ex}}(x,y,z) - \mathrm{HU}_{\mathrm{in}}\{x+u_x(x,y,z), y+u_y(x,y,z), z+u_z(x,y,z)\}}{\mathrm{HU}_{\mathrm{in}}\{x+u_x(x,y,z), y+u_y(x,y,z), z+u_z(x,y,z)\}+1000}\mathrm{Vol}_{\mathrm{ex}}^{\mathrm{voxel}}(x,y,z). \quad (3)$$

Given that $\mathrm{Vol}_{\mathrm{ex}}^{\mathrm{voxel}}$ is identical for all voxels, the HU change-based ventilation metric (V_{4DCT}^{HU}) has been defined as:

$$V_{4DCT}^{HU}(x,y,z) = \frac{\mathrm{HU}_{\mathrm{ex}}(x,y,z) - \mathrm{HU}_{\mathrm{in}}\{x+u_x(x,y,z), y+u_y(x,y,z), z+u_z(x,y,z)\}}{\mathrm{HU}_{\mathrm{in}}\{x+u_x(x,y,z), y+u_y(x,y,z), z+u_z(x,y,z)\}+1000}. \quad (4)$$

Furthermore, the CT density scaling factor ρ_{scaling} has been added to Equation (4) as described in detail in the Methods and Materials section.

The Jacobian determinant (J) of the displacement vector u is given by

$$J(x,y,z) = \begin{vmatrix} 1+\frac{\partial u_x(x,y,z)}{\partial x} & \frac{\partial u_x(x,y,z)}{\partial y} & \frac{\partial u_x(x,y,z)}{\partial z} \\ \frac{\partial u_y(x,y,z)}{\partial x} & 1+\frac{\partial u_y(x,y,z)}{\partial y} & \frac{\partial u_y(x,y,z)}{\partial z} \\ \frac{\partial u_z(x,y,z)}{\partial x} & \frac{\partial u_z(x,y,z)}{\partial y} & 1+\frac{\partial u_z(x,y,z)}{\partial z} \end{vmatrix}. \quad (5)$$

The volume of voxel deformed into the inhale phase ($\mathrm{Vol}_{\mathrm{in}}^{\mathrm{voxel}}$) can be estimated by

$$\mathrm{Vol}_{\mathrm{in}}^{\mathrm{voxel}} = \mathrm{Vol}_{\mathrm{ex}}^{\mathrm{voxel}} J(x,y,z). \quad (6)$$

The exhale-to-inhale volume change ($\Delta\mathrm{Vol}$) is expressed as

$$\Delta \mathrm{Vol} = \mathrm{Vol}_{\mathrm{in}}^{\mathrm{voxel}} - \mathrm{Vol}_{\mathrm{ex}}^{\mathrm{voxel}} = \mathrm{Vol}_{\mathrm{ex}}^{\mathrm{voxel}}\{J(x,y,z)-1\}. \quad (7)$$

Given that $\mathrm{Vol}_{\mathrm{ex}}^{\mathrm{voxel}}$ is identical for all voxels, the Jacobian-based ventilation metric (V_{4DCT}^{Jac}) has been defined as:

$$V_{4DCT}^{Jac}(x,y,z) = J(x,y,z) - 1. \quad (8)$$

Furthermore, the CT density scaling factor ρ_{scaling} has been added to Equation (8) as described in detail in the Methods and Materials section.

[1] Simon BA. Non-invasive imaging of regional lung function using x-ray computed tomography. *J Clin Monit Comput* 2000;16:433-442.

[2] Guerrero T, Sanders K, Noyola-Martinez J, et al. Quantification of regional ventilation from treatment planning CT. *Int J Radiat Oncol Biol Phys* 2005;62:630-634.

[3] Hoffman EA Ritman EL. Effect of body orientation on regional lung expansion in dog and sloth. *J Appl Physiol* 1985;59:481-491.