A database of virtual healthy subjects: Reference Manual

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1 Brief description of the study

We present a novel methodology to assess theoretically physiological computed indices and tools based on pulse wave analysis (Figure 1). We have created a database of virtual healthy adult subjects using a validated one-dimensional numerical model of the arterial hemodynamics, which cardiac and arterial parameters are varied within physiological healthy ranges (Table 1). The generated set of simulations encloses more than 3000 cases which could be encountered in a clinical study. For each simulation, hemodynamic signals (e.g. pressure, flow and distension waveforms) are available at all arterial locations, and allow the computation of indices of interest. In our initial study [1], we have focused on the particular application of central and peripheral foot-to-foot pulse wave velocities.

Parameter p		Variation v (%)	Factor f (-)
Elastic arteries PWV	c_{el}	-19, 0, +30, +60, +90, +125	×0.81, ×1.0, ×1.3, ×1.6, ×1.9, ×2.25
Muscular arteries PWV	c_{musc}	-20, 0, +15, +30	×0.8, ×1.0, ×1.15, ×1.3
Elastic arteries diameter	D_{el}	-10, 0, +20, +40	×0.9, ×1.0, ×1.2, ×1.4
Muscular arteries diameter	D_{musc}	-10, 0, +21	×0.9, ×1.0, ×1.21
Heart rate	HR	-15, 0, +15	×0.85, ×1.0, ×1.15
Stroke volume	SV	-20, 0, +20	×0.8, ×1.0, ×1.2
Peripheral vascular resistance	PVR	-10, 0, +10	×0.9, ×1.0, ×1.1

Table 1: Incremental variations based on clinical observations within a healthy population of the seven parameters considered in this study. The variations of each parameters are expressed as the increase/decrease in % of the baseline value (v), and as a multiplication factor (f).

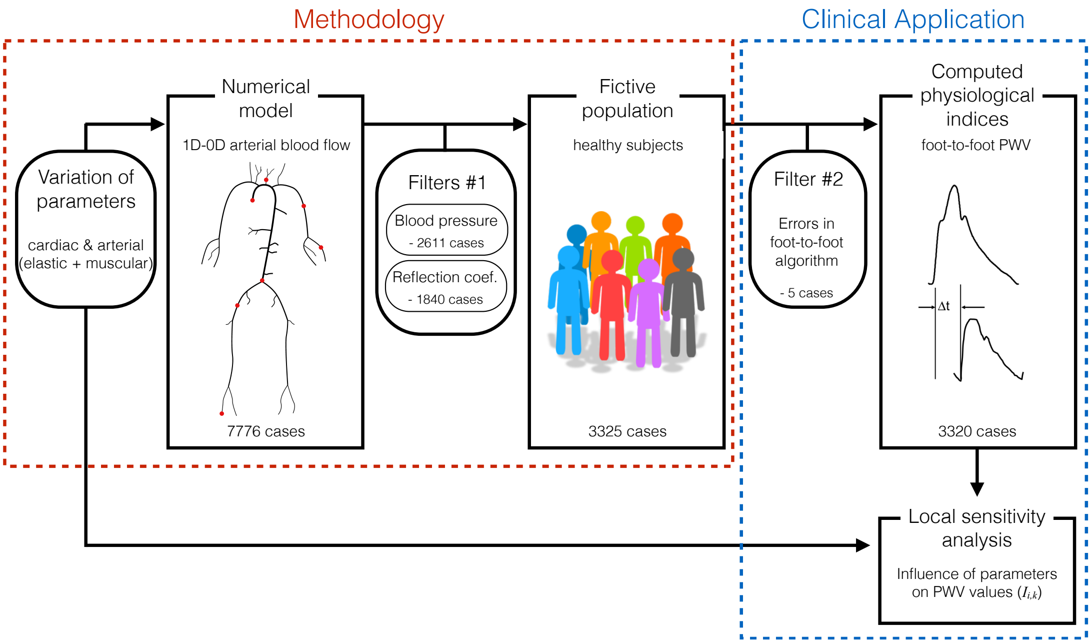

Figure 1: Our study consists of two parts: the development of a new methodology (i.e. the creation of a database) and its clinical application (i.e. the assessment of foot-to-foot PWV). By varying the cardiac and arterial parameters of the 1D-0D model within healthy ranges, we create a set of 7776 simulations. Rejection criteria (Filters #1) are applied in order to eliminate non-physiological data, which reduce the database to 3325 cases. Using that numerical database, we compute the physiological index of interest (i.e. foot-to-foot PWV) and additionally reject cases with failure of the PWV algorithm (Filter #2). Peripheral and central PWV indices are computed for each of the 3320 cases of our fictive database, using pressure waves observed at the red dots in the 1D model. We further compute an index of local sensitivity analysis $\bar{I}_{i,k}$ that describes the effect of parameters variation on PWV values.

2 Description of the hemodynamic data

Data is saved in Matlab formatted binary files (`.mat`). It can be divided into 3 categories:
(i) general data relative to the arterial network geometry,
(ii) hemodynamics signals relative to each simulated case, and
(iii) computed physiological indices of interest.
In addition, data is divided into the physiological cases (#3325 cases, `PHYSIO`) and the non-physiological ones (#4451 cases, `NOTPHYSIO`), according the filtering criteria #1 in Figure 1.

The arterial tree used to generate the population is sketched in Figure 2. We provide hemodynamic data for each fictive subject of the database at 11 points within the arterial network. Each artery is given a variable name, as described in Table 2.

Artery	Variable name (`<ARTERY>`)
Aortic root	`AORTA_ROOT`
Ascending aorta	`AORTA_ASC`
Descending aorta	`AORTA_DESC`
Thoracic aorta	`AORTA_THO`
Carotid	`CAROTID`
Brachial	`BRACHIAL`
Radial	`RADIAL`
Aorto-iliac bifurcation	`BIFURCATION`
Iliac	`ILIAC`
Femoral	`FEMORAL`
Anterior tibial (ankle)	`ANT_TIBIAL`

Table 2: Variable name for the 11 arteries where data is available.

The hemodynamic variables are defined as follows with their units. The time step for hemodynamic signals is `dt = 0.001 s`.

t	Time	s	SBP	Systolic Blood Pressure	mmHg
P	Pressure	Pa	DBP	Diastolic Blood Pressure	mmHg
Q	Flow	m^3/s	MBP	Mean Blood Pressure	mmHg
A	Area	m^2	PP	Pulse Pressure	mmHg

2.1 General data

Table 3 presents the geometry of the 55-artery network at baseline: length, end-diastolic inlet and outlet diameters, and end-diastolic pulse wave velocities of each arteries. In addition, resistance and compliance Windkessel parameters are listed. Note that `Nektar` is the name of the numerical code used in our study. Details on the computation of some parameters is provided in Section 4.

The Matlab file `Fictive_database.mat` contains the structure `NETWORK` which details the location of the 11 observation points within the arterial network:

`NETWORK.<ARTERY>.LengthFromHeart`	Length from the aortic valve [m]
`.LengthInSegment`	Length from the origin of the arterial segment [m]
`.NektarSegment`	Number of the arterial segment in Nektar [-]

2.2 Hemodynamic data

At each arterial location, a Matlab binary file stores the hemodynamic data for the physiological cases (<ARTERY>_physio.mat). For completeness, we also further provide the data for the non-physiological cases (<ARTERY>_notPhysio.mat). The structure saved within each mat file is named <ARTERY>_PHYSIO or <ARTERY>_NOTPHYSIO and is organised as an array of n structures {...} (with n = 3325 for physiological cases, n = 4451 for non-physiological cases):

```
<ARTERY>_PHYSIO = [ {1}, {...}, ... , {i}, ... , {...}, {n} ]
```

Each structure corresponds to one fictive case (i):

```
<ARTERY>_PHYSIO{i}.ONE_CYCLE     = <SIGNALS> :  Signals during one cardiac cycle
                  .MORE_CYCLES   = <SIGNALS> :  Signals during 5 s
                  .parameters    = <PARAM> :    Multiplication factors f of parameters
                                                and corresponding elastic modulus
                  .heart.T       = <Number> :   Cardiac period (s)
                  .heart.SV      = <Number> :   Stroke Volume (ml)
                  .physio        = <Boolean> :  true if physiological case
                  .algoPWV_ok    = <Boolean> :  true if foot-to-foot PWV
                                                algorithm succeeded
```

The sub-structures are defined as follows:

```
<SIGNALS> = <4-columns Array> :  [t P Q A]

<PARAM>.PWV_el    = <Number> : f of elastic arteries PWV
       .PWV_musc  = <Number> : f of muscular arteries PWV
       .D_el      = <Number> : f of elastic arteries diameter
       .D_musc    = <Number> : f of muscular arteries diameter
       .HR        = <Number> : f of Cardiac Period (NOT heart rate!)
       .SV        = <Number> : f of stroke volume
       .PVR       = <Number> : f of peripheral vascular resistance
       .E_el      = <Number> : f of elastic modulus of elastic arteries
       .E_musc    = <Number> : f of elastic modulus of muscular arteries
```

2.3 Computed Indices

Computed indices are stored in the structures COMPUTED_PHYSIO and COMPUTED_NOTPHYSIO for physiological and non-physiological cases respectively. These are saved within the file Fictive_database.mat and are organised as follows:

```
COMPUTED_PHYSIO.PARAMETERS     = <Array (nx9)>:     Multiplication factors for all n cases
               .INDICES        = [{...}, {i}, {...}]: Indices computed from waveforms
               .PWV_PATH       = [{...}, {i}, {...}]: PWV values along arterial path
               .SENSITIVITY    = <SA>:              Sensitivity Analysis results

COMPUTED_NOTPHYSIO.PARAMETERS  = <Array (nx9)>:     Multiplication factors for all n cases
                  .INDICES     = [{...}, {i}, {...}]: Indices computed from waveforms
                  .PWV_PATH    = [{...}, {i}, {...}]: PWV values along arterial path
```

The sub-structures are defined as follows:

.PARAMETERS summarises the values of the multiplication factors f for the 7 parameters and corresponding 2 elastic moduli, for all n cases considered.

.PARAMETERS(i,:) $= [c_{\mathrm{el}} \quad c_{\mathrm{musc}} \quad D_{\mathrm{el}} \quad D_{\mathrm{musc}} \quad \mathrm{HR} \quad \mathrm{SV} \quad \mathrm{PVR} \quad E_{\mathrm{el}}\ E_{\mathrm{musc}}]$

.INDICES{i} stores indices extracted from hemodynamic waveforms:

.INDICES{i}.CO	= <Number>:	Cardiac Output (l/min)
.ABI	= <Number>:	Ankle-Brachial Index (-)
.PPA	= <Number>:	Pulse Pressure Amplification (-)
.ReflCoef	= <Number>:	Reflection coefficient at aorto-iliac bifurcation (-)
.Pressures.aortic_root	= <Ix_P>:	Pressures at aortic root (mmHg)
.Pressures.carotid	= <Ix_P>:	Pressures at carotid (mmHg)
.Pressures.brachial	= <Ix_P>:	Pressures at brachial (mmHg)

<IX_P> = [SBP DBP MBP PP]

.PWV_PATH{i} stores pulse wave velocities (PWV) over an arterial path.

.PWV_PATH{i}.FootToFoot	= <PWVs>:	PWV computed with algorithm, $\mathrm{PWV}_{\mathrm{ff}}$ (m/s)
.Theoretical	= <PWVs>:	PWV assessed theoretically, $\mathrm{PWV}_{\mathrm{th}}$ (m/s)

<PWVs> = <Array (1x6)>

$$= \begin{bmatrix} \text{aPWV} & \text{aortic PWV (aortic root to iliac bifurcation)} \\ \text{cfPWV} & \text{carotid-femoral(iliac) PWV} \\ \text{faPWV} & \text{femoral(iliac)-ankle PWV} \\ \text{baPWV} & \text{brachial-ankle PWV} \\ \text{crPWV} & \text{carotid-radial PWV} \\ \text{hfPWV} & \text{heart-femoral(iliac) PWV} \end{bmatrix}^{\mathsf{T}}$$

.SENSITIVITY stores results of the sensitivity analysis of PWV to parameters variation. This result is only available for physiological cases.

<SA>.FootToFoot	= <SA_IX>:	using PWV computed with algorithm
.Theoretical	= <SA_IX>:	using PWV assessed theoretically

<SA_IX>.IndexMean	= <Array (6x7)>:	Average relative sensitivity index ($\bar{I}_{i,k}$) of parameter i ($i \in [1:7]$) to output PWV_k ($k \in [1:6]$)
.IndexSD	= <Array (6x7)>:	Standard deviation of $\bar{I}_{i,k}$

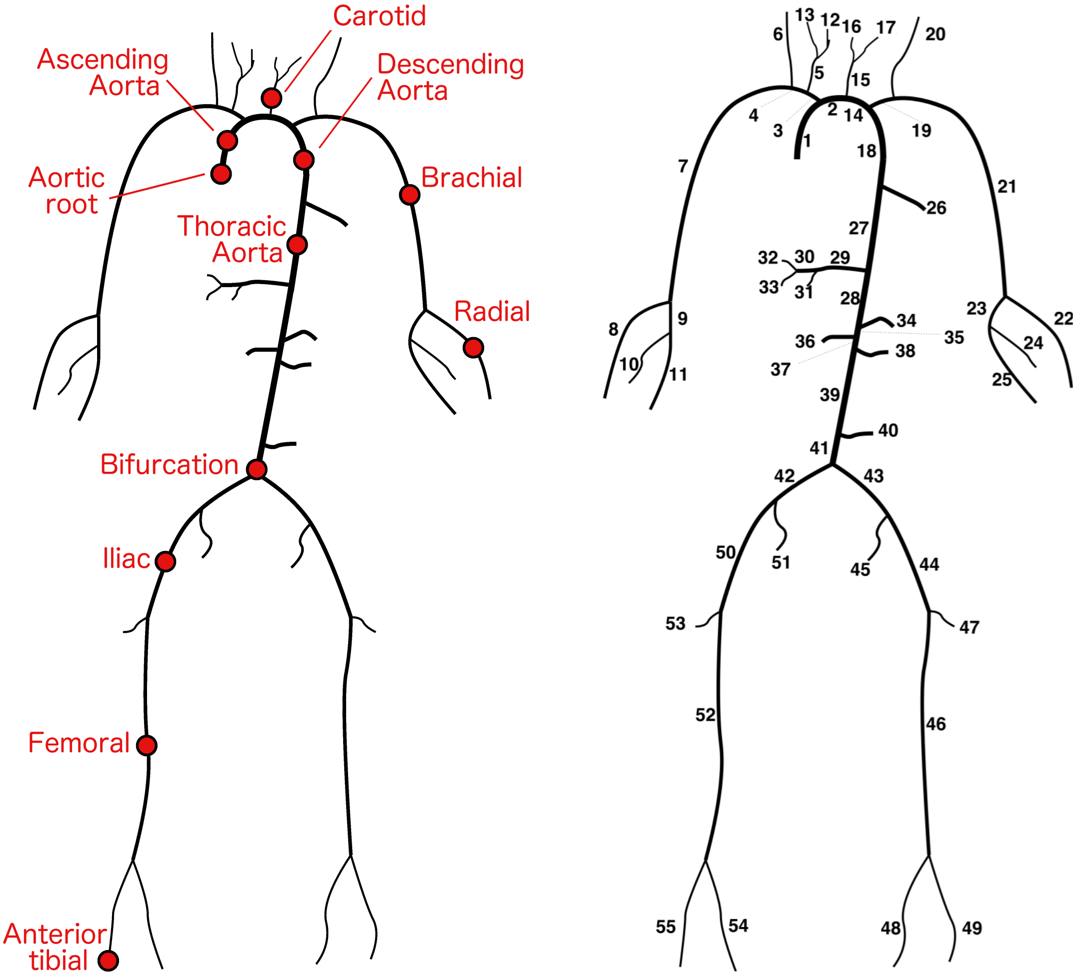

Figure 2: Sketchs of the 55-artery network used to generate the fictive database: (left) with highlight of the 11 locations where hemodynamic data is available, and (right) with details on the numbering of arteries.

Arterial segment	Length L (cm)	Prescribed Diam. $D^*_{\mathrm{d,in}} \to D^*_{\mathrm{d,out}}$ (mm)	Computed Diam. $D_{\mathrm{d,in}} \to D_{\mathrm{d,out}}$ (mm)	Pulse wave velocity a -	$c_{\mathrm{in}} \to c_{\mathrm{out}}$ (m/s)	Peripheral resistance R (10^{10} Pa s m^{-3})	Peripheral compliance C (10^{-10} m^3 Pa^{-1})
1. Ascending aorta	5.8	30.3 → 30.2	27.6 → 27.4	14.3	4.9 → 4.91	-	-
2. Aortic arch A	2.3	25.8 → 24.7	23.7 → 22.7	14.3	5.16 → 5.24	-	-
3. Brachiocephalic	3.9	20.8 → 18.5	19.3 → 17.3	14.3	5.54 → 5.75	-	-
4. R. subclavian	3.9	11.8 → 9.27	11.2 → 8.85	14.3	6.63 → 7.16	-	-
5. R. common carotid	10.8	11.3 → 5.86	10.7 → 5.66	14.3	6.73 → 8.26	-	-
6. R. vertebral	17.1	3.81 → 2.88	3.72 → 2.82	15.6	10.3 → 11.2	0.451	0.902
7. R. brachial	48.5	8.34 → 4.84	8.04 → 4.7	15.6	8.11 → 9.58	-	-
8. R. radial	27	3.81 → 3.19	3.72 → 3.11	15.6	10.3 → 10.9	0.396	0.987
9. R. ulnar A	7.7	3.81 → 3.5	3.72 → 3.42	15.6	10.3 → 10.6	-	-
10. R. interosseous	9.1	2.16 → 1.85	2.12 → 1.82	15.6	12.3 → 12.9	6.32	0.325
11. R. ulnar B	19.7	3.29 → 2.88	3.22 → 2.81	15.6	10.8 → 11.2	0.396	0.769
12. R. internal carotid	20.5	5.87 → 4.42	5.7 → 4.31	15.6	9.04 → 9.85	0.188	2.58
13. R. external carotid	18.7	2.57 → 1.54	2.53 → 1.52	15.6	11.6 → 13.6	1.04	1.93
14. Aortic arch B	4.5	22 → 21.4	20.4 → 19.8	14.3	5.44 → 5.48	-	-
15. L. common carotid	16	10 → 5.02	9.56 → 4.85	14.3	6.99 → 8.67	-	-
16. L. internal carotid	20.5	4.43 → 3.43	4.32 → 3.34	15.6	9.85 → 10.6	0.188	1.89
17. L. external carotid	18.7	1.97 → 1.26	1.94 → 1.23	15.6	12.6 → 14.4	1.04	1.73
18. Thoracic aorta A	6	20.6 → 19.5	19.1 → 18.1	14.3	5.55 → 5.65	-	-
19. L. subclavian	3.9	11.3 → 8.76	10.7 → 8.37	14.3	6.72 → 7.29	-	-
20. L. vertebral	17	3.81 → 2.88	3.72 → 2.82	15.6	10.3 → 11.2	0.451	0.902
21. L. brachial	48.5	8.34 → 4.84	8.04 → 4.7	15.6	8.11 → 9.58	-	-
22. L. radial	27	3.6 → 2.88	3.52 → 2.82	15.6	10.5 → 11.2	0.396	0.848
23. L. ulnar A	7.7	4.43 → 4.43	4.31 → 4.31	15.6	9.85 → 9.85	-	-
24. L. interosseous	9.1	1.85 → 1.85	1.82 → 1.82	15.6	12.9 → 12.9	6.32	0.277
25. L. ulnar B	19.7	4.22 → 3.81	4.11 → 3.71	15.6	9.99 → 10.3	0.396	1.3
26. Intercostals	9.2	13 → 9.78	12.2 → 9.31	14.3	6.44 → 7.04	0.6	10.4
27. Thoracic aorta B	12	17 → 13.3	15.9 → 12.5	14.3	5.91 → 6.39	-	-
28. Abdominal aorta A	6.1	12.6 → 12.6	11.8 → 11.8	14.3	6.5 → 6.5	-	-
29. Celiac A	2.3	8.03 → 7.1	7.68 → 6.82	14.3	7.49 → 7.78	-	-
30. Celiac B	2.3	5.35 → 5.04	5.17 → 4.88	14.3	8.49 → 8.65	-	-
31. Hepatic	7.6	5.56 → 4.53	5.4 → 4.41	15.6	9.19 → 9.78	0.272	2.05
32. Gastric	8.2	3.29 → 3.09	3.22 → 3.02	15.6	10.8 → 11	0.406	0.821
33. Splenic	7.2	4.32 → 4.02	4.21 → 3.91	15.6	9.92 → 10.1	0.174	1.4
34. Superior mesenteric	6.8	8.13 → 7.31	7.77 → 7	14.3	7.45 → 7.71	0.0698	4.81
35. Abdominal aorta B	2.3	11.8 → 11.6	11.2 → 11	14.3	6.62 → 6.66	-	-
36. L. renal	3.7	5.35 → 5.35	5.17 → 5.16	14.3	8.49 → 8.49	0.0848	2.31
37. Abdominal aorta C	2.3	12.1 → 12.1	11.5 → 11.5	14.3	6.57 → 6.57	-	-
38. R. renal	3.7	5.35 → 5.35	5.17 → 5.16	14.3	8.49 → 8.49	0.0848	2.31
39. Abdominal aorta D	12.2	11.9 → 11.3	11.3 → 10.7	14.3	6.6 → 6.71	-	-
40. Inferior mesenteric	5.8	4.84 → 3.28	4.7 → 3.21	15.6	9.58 → 10.8	0.516	1.33
41. Abdominal aorta E	2.3	11.1 → 10.7	10.5 → 10.1	14.3	6.75 → 6.83	-	-
42. L. common iliac	6.8	8.13 → 7.2	7.9 → 7.01	18	9.47 → 9.83	-	-
43. R. common iliac	6.8	8.13 → 7.2	7.9 → 7.01	18	9.47 → 9.83	-	-
44. L. external iliac	16.6	6.59 → 6.28	6.42 → 6.12	18	10.1 → 10.2	-	-
45. L. internal iliac	5.8	4.12 → 4.12	4.05 → 4.05	19.7	12.8 → 12.7	0.596	1.37
46. L. femoral	50.9	5.35 → 3.91	5.25 → 3.85	19.7	11.8 → 12.9	-	-
47. L. deep femoral	14.5	4.12 → 3.81	4.05 → 3.75	19.7	12.7 → 13.1	0.358	1.27
48. L. posterior tibial	36.9	3.19 → 2.88	3.14 → 2.84	19.7	13.8 → 14.2	1.06	0.743
49. L. anterior tibial	39.8	2.68 → 2.37	2.64 → 2.33	19.7	14.5 → 15.1	1.06	0.513
50. R. external iliac	16.6	6.59 → 6.28	6.42 → 6.12	18	10.1 → 10.2	-	-
51. R. internal iliac	5.8	4.12 → 4.12	4.05 → 4.05	19.7	12.8 → 12.7	0.596	1.37
52. R. femoral	50.9	5.35 → 3.91	5.25 → 3.85	19.7	11.8 → 12.9	-	-
53. R. deep femoral	14.5	4.12 → 3.81	4.05 → 3.75	19.7	12.7 → 13.1	0.358	1.27
54. R. posterior tibial	36.9	3.19 → 2.88	3.14 → 2.84	19.7	13.8 → 14.2	1.06	0.743
55. R. anterior tibial	39.8	2.68 → 2.37	2.64 → 2.33	19.7	14.5 → 15.1	1.06	0.513

Table 3: End-diastolic parameters of the baseline model: arterial length L, prescribed cross-sectional diameter D^*_{d}, computed cross-sectional diameter D_{d}, pulse wave velocity coefficient a and value c, resistance $R = R_1 + R_2$ and compliance C of the peripheral Windkessel models. The subscripts *in* and *out* refer to the inlet and outlet of the arterial segment, modelled as linearly tapered. The arterial network is sketched in Figure 2.

3 Search tools

We provide search tools (Matlab functions) that return subject indexes depending on the value of their parameters and computed indices. Details on inputs and outputs of the functions are specified in the headers of the Matlab files.

- Function `search_DB_param.m`: Returns the index of the subject with variations v specified for all 7 parameters `[`$\mathtt{c}_{\text{elastic}}$ $\mathtt{c}_{\text{muscular}}$ $\mathtt{D}_{\text{elastic}}$ $\mathtt{D}_{\text{muscular}}$ `HR SV PVR]`.
- Function `search_DB_indices.m`: Return the indexes of subjects presenting the computed indexes `CO, ABI, PPA` or `ReflCoef` with value within specified interval.
- Function `search_DB_pressures.m`: Return the indexes of subjects presenting a pressure value `SBP, DBP, MBP` or `PP` at specified location (aortic root, brachial or carotid), with value within specified interval.
- Function `search_DB_PWV.m`: Return the indexes of subjects presenting a pulse wave velocity value computed using `foot-to-foot` or `theoretical` algorithm along specified path (`aPWV`, `cfPWV`, `faPWV`, `baPWV`, `crPWV` or `hfPWV`), with PWV value within specified interval.

Examples of these functions are provided in the matlab file `SearchTools.m`.

4 Details on the computation of some model parameters

These notes help to clarify the definition of the model variables, as described in the Appendix of [1]. We define the following variables:

$A(x,t)$: Cross-sectional area of the vessel, at the location x and time t
$A_0(x)$: Initial value of area at time $t = 0$ and location x
$A_\text{d}(x)$: *Computed* end-diastolic area at location x
$A^*_\text{d}(x)$: *Prescribed* end-diastolic area at location x
P^*_d: *Prescribed* end-diastolic pressure
P_ext: External pressure

Note that $A^*_\text{d}(x)$ is the expected diastolic area, and is different from the computed diastolic area $A_\text{d}(x)$.

Initiation of the variables β and A_0
With the definition of these variables, the elastic tube law can be written as:

$$P(x,t) = P_\text{ext} + \frac{\beta}{A^*_\text{d}}\left(\sqrt{A(x,t)} - \sqrt{A^*_\text{d}}\right) \tag{1}$$

with $\beta(x)$ describing the material properties at each location x:

$$\beta(x) = \frac{4}{3}\sqrt{\pi}Eh = \frac{2\ \rho\ c^2 A^*_\text{d}}{\sqrt{A}} \tag{2}$$

$\beta(x)$ is constant in time and computed at $t = 0$ using the prescribed diastolic area A_d^*:

$$\beta(x) = \frac{2\ \rho\ c^2 A_\mathrm{d}^*}{\sqrt{A_\mathrm{d}^*}} \tag{3}$$

and using the empirical law for c (Equation 11 of [1]):

$$\beta(x) = \frac{2\ \rho\ A_\mathrm{d}^*}{\sqrt{A_\mathrm{d}^*}} \left(\frac{a}{(D_\mathrm{d}^*)^b}\right)^2 \tag{4}$$

$$\text{with}\ \ D_\mathrm{d}^* = \sqrt{\frac{4A_\mathrm{d}^*}{\pi}}\quad \text{(only) expressed in } mm \tag{5}$$

Values of the baseline coefficients a and prescribed end-diastolic diameter D_d^* are listed in Table 3; the coefficient $b = 0.3$ and the external pressure $P_\mathrm{ext} = 0$ mmHg. *Note that Table 3 presents the corrected variable values in comparison with Table A.1 in [1].* For each simulation in the database, values of the coefficients a^v and variables $D_\mathrm{d}^*|^v$ are computed using the baseline values (a^0 and $D_\mathrm{d}^*|^0$) and the variation amplitudes v or factors f described in Table 1:

$$a^v = a^0\,(1 + v_c/100) = a^0\, f_c \tag{6}$$

$$D_\mathrm{d}^*|^v = D_\mathrm{d}^*|^0\,(1 + v_D/100) = D_\mathrm{d}^*|^0\, f_D \tag{7}$$

At $t = 0$, we define as initial conditions that $(A, U, P) = (A_0, 0, 0)$ in all segments. A_0 is the area that yields the prescribed end-diastolic area A_d^* at $P_\mathrm{ext} = P_\mathrm{d}^*$. Therefore, the tube law becomes:

$$0 = P_\mathrm{d}^* + \frac{\beta}{A_\mathrm{d}^*}(\sqrt{A_0} - \sqrt{A_\mathrm{d}^*}) \tag{8}$$

such that A_0 can be computed as:

$$A_0 = \left(\sqrt{A_\mathrm{d}^*} - \frac{P_\mathrm{d}^* A_\mathrm{d}^*}{\beta}\right)^2. \tag{9}$$

Instantaneous PWV $c(x, t)$:
Using Eq. (2), the instantaneous value of the PWV c at a location x and time t can be calculated as:

$$c(x, t) = \sqrt{\frac{\beta(x)}{2\rho\ A_\mathrm{d}^*}}\ A(x, t)^{1/4} \tag{10}$$

References

[1] M. Willemet, P. Chowienczyk, and J. Alastruey. A database of virtual healthy subjects to assess the accuracy of foot-to-foot pulse wave velocities for estimation of aortic stiffness. *American Journal of Physiology - Heart and Circulatory Physiology*, doi: 10.1152/ajpheart.00175.2015, 2015.