Modeling Inter-individual Variation in Physiological Factors Used in PBPK Models of Humans

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Abstract

Modeling interindividual variation in internal dose in humans using PBPK models requires data on the variation in the physiological parameters across the population of interest. These data should also capture the correlations between the values in each person. In this project, we developed a tool to provide such data and its correlations. The tool provides a source of data for human physiological parameters where 1) the parameter values for an individual are correlated with one another, and 2) values of parameters vary according to interindividual variation in the general population, by gender, race, and age. The parameters investigated in this project include: 1) volumes of selected organs and tissues; 2) blood flows for the organs and tissues; and 3) the total cardiac output under resting conditions and average daily inhalation rates. These parameters are expressed as records of correlated values for the approximately 30,000 individuals evaluated in the NHANES III survey. Software was developed that allows records to be retrieved randomly from the database with specification of constraints on, age, sex, and ethnicity. The database and accompanying software together provide a convenient tool for parameterization of human PBPK models for the study of interindividual variation. In addition, the data provides a useful information on the variation in physiological parameters in adults and children. This work was funded by the American Chemistry Council.

Approach

This project developed a database of physiological parameters for use in PBPK models and exposure assessments. The database consists of a series of "records". Each record contains a set of internally consistent values. Records are created based on data from the individuals who participated in The Third National Health and Nutrition Examination Survey (NHANES III). NHANES III provides data on key physiological parameters on each individual that capture correlations of height, weight, and other factors. The survey data also provide the basis for estimating unmeasured physiological parameters using published models of organ volume and blood flow. The result is a database consisting of approximately 30,000 records. Each record includes:

1. The age, gender, and ethnicity of the individual.
2. Volumes and masses of selected organs and tissues;
3. Blood flows to the organs and tissues; and
4. Total resting cardiac output,
5. Surface area, and
6. Average inhalation rate.

Finally, a computer program (Physiological Parameters for PBPK Modeling (PPPM or P³M) generates "sets" of the records for groups of individuals of specific age ranges, gender, and ethnicity.

Mass Check

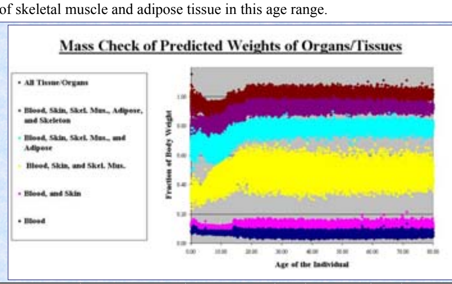
The estimated volumes are the product of more than 30 equations developed independently. A check was performed to see if the predicted volumes are reasonable. The check was performed using the following steps:

- Convert volumes to their equivalent weights (using organ specific densities),
- Summing the weights, and
- Divide the total by the reported body weight.

Values close to 1.0 indicate that predicted values are internally consistent.

Mass Check Results

The mass check indicates a good fit for adults and small underestimation of volumes in children ages 8-12. This may reflect a limited data on the volume of skeletal muscle and adipose tissue in this age range.

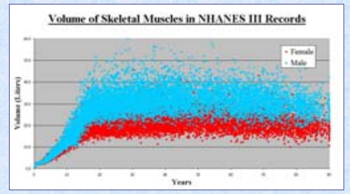


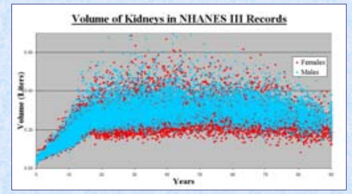
Organ Specific Perfusion Rates (l/min/l)

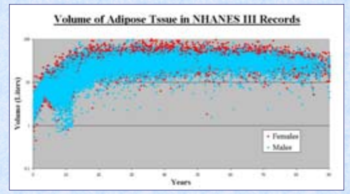
	Cowles et al.1971	Fis.-Berg. and Hughes (1983)	Will. & Leg., (1989)		Values Used in This Project	
Organ	Male and Female	Male	Male	Female	Male	Female
Thyroid	5	3.57	-	-	5	5
Kidneys	3.96	3.96	3.7	3.22	3.7	3.22
Heart	0.806	0.81	0.7	0.96	0.7	0.96
Brain	0.529	0.53	0.5	0.52	0.5	0.52
Splanchnic Tissues	0.038	-	-	-	-	-
Liver	-	0.58	0.8	1	0.8	1
Pancreas	-	-	0.6	0.61	0.6	0.61
Spleen	-	-	1	1.04	1	1.04
GI Organs	-	0.37	0.8	0.78	0.8	0.78
Skin	0.057	0.09	0.1	0.15	0.1	0.15
Muscle	0.0212	0.05	0	0.03	0	0.03
Skeleton	-	-	0	0.03		
Red Marrow	0.399	-	-	-	0.3	0.3
Yellow Marrow	0.028	0.03	-	-	0	0.03
Bone tissue	-	0.01	-	-	-	-
Adipose Tissue	0.0241	0.03	0	0.03	0	0.03

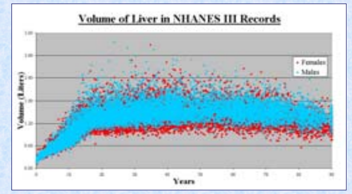
Results

Predicted Volumes for Select Tissues and Organs









Predicted Values of Physiological Parameters

	Children Ages 4-6			Adult Males (25-35)			Adult Females (25-35)		
	Mean	Std. Dev.	CV	Mean	Std. Dev.	CV	Mean	Std. Dev	CV
Weight (kg)	19	3.7	0.19	80	17	0.21	69	18	0.25
Height (cm)	109.5	6.1	0.056	174.3	7.6	0.044	161	7.1	0.04
Hematocrit (unitless)	0.37	0.022	0.060	0.45	0.027	0.060	0.39	0.029	0.074
Resistance (ohm)	-	-	-	482	64	0.13	584	80	0.14
Total Well Perf. Vol. (l)	3.2	0.43	0.14	7.5	0.95	0.13	6.8	0.99	0.14
Red Marrow Vol. (l)	0.43	0.11	0.25	1.5	0.25	0.16	1.0	0.18	0.18
Lungs Vol. (l)	0.24	0.039	0.16	0.98	0.12	0.13	0.86	0.12	0.14
Brain Vol. (l)	1.4	0.15	0.11	1.3	0.046	0.035	1.2	0.043	0.037
Kidneys Vol. (l)	0.10	0.015	0.15	0.30	0.064	0.21	0.26	0.067	0.25
Liver Vol. (l)	0.50	0.074	0.15	1.5	0.24	0.16	1.4	0.26	0.19
Pancreas Vol. (l)	0.034	0.0050	0.14	0.096	0.016	0.17	0.086	0.016	0.19
Spleen Vol. (l)	0.069	0.010	0.15	0.21	0.035	0.16	0.19	0.038	0.20
Thyroid Vol. (l)	0.0053	0.00083	0.16	0.019	0.0033	0.17	0.018	0.0034	0.19
GI Organs Vol. (l)	0.28	0.044	0.16	1.2	0.20	0.17	1.2	0.22	0.19
Blood Vol. (l)	1.5	0.22	0.15	5.7	0.63	0.11	4.1	0.43	0.11
Plasma Vol. (l)	0.97	0.15	0.15	3.4	0.40	0.12	2.6	0.30	0.11
Blood Cell Vol. (l)	0.49	0.082	0.17	2.3	0.29	0.13	1.4	0.18	0.13
Total Poorly Perf. Vol. (l)	5.5	0.91	0.16	35	5.6	0.16	25	4.4	0.18
Dermis Vol. (l)	0.52	0.059	0.11	3.6	0.41	0.11	3.2	0.43	0.13
Epidermis Vol. (l)	0.060	0.0068	0.11	0.16	0.018	0.11	0.14	0.019	0.13
Skeletal Muscle Vol. (l)	4.8	0.83	0.17	30	5.2	0.17	21	3.9	0.19
Heart Vol. (l)	0.11	0.015	0.14	0.35	0.048	0.14	0.30	0.042	0.14
Tongue Vol. (l)	0.023	0.0044	0.20	0.095	0.020	0.21	0.082	0.021	0.25
Total Fatty Tissues Vol. (l)	7.3	2.5	0.34	31	12	0.38	35	14	0.39
Adipose Tissue Vol. (l)	7.05	2.4	0.35	28	12	0.42	33	13	0.41
Yellow Marrow Vol. (l)	0.23	0.075	0.32	3.3	0.55	0.16	2.3	0.40	0.18
Bone tissue Vol. (l)	1.00	0.24	0.24	3.9	0.65	0.17	2.6	0.48	0.18
Total Well Perf. Bl. Flow (l/min)	1.97	0.26	0.13	4.8	0.71	0.15	4.4	0.76	0.17
Red Marrow Bl. Flow (l/min)	0.13	0.032	0.24	0.45	0.075	0.16	0.31	0.055	0.18
Brain Bl. Flow (l/min)	0.72	0.076	0.11	0.68	0.0016	0.0025	0.63	0.0016	0.0025
Kidneys Bl. Flow (l/min)	0.33	0.055	0.17	1.1	0.24	0.21	0.85	0.21	0.25
Liver Bl. Flow (l/min)	0.46	0.078	0.17	1.3	0.21	0.16	1.4	0.26	0.19
Pancreas Bl. Flow (l/min)	0.021	0.0030	0.15	0.057	0.0098	0.17	0.052	0.0097	0.19
Thyroid Bl. Flow (l/min)	0.026	0.0039	0.15	0.096	0.016	0.17	0.092	0.017	0.19
Spleen Bl. Flow (l/min)	0.070	0.011	0.15	0.21	0.035	0.16	0.20	0.039	0.20
GI Organs Bl. Flow (l/min)	0.22	0.034	0.16	0.89	0.15	0.17	0.90	0.17	0.19
Total Poorly Perf. Bl. Flow (l/min	0.31	0.050	0.16	1.63	0.24	0.15	1.4	0.22	0.16
Dermis Bl. Flow (l/min)	0.070	0.011	0.16	0.43	0.049	0.11	0.49	0.065	0.13
Epidermis Bl. Flow (l/min)	0.0081	0.0013	0.16	0.019	0.0022	0.11	0.021	0.0029	0.13
Skeletal Muscle Bl. Flow (l/min)	0.14	0.025	0.17	0.91	0.16	0.17	0.63	0.12	0.19
Heart Bl. Flow (l/min)	0.090	0.018	0.20	0.26	0.035	0.14	0.29	0.041	0.14
Tongue Bl. Flow (l/min)	0.00068	0.00013	0.20	0.0028	0.00060	0.21	0.0025	0.00063	0.25
Total Fat Bl. Flow (l/min)	0.18	0.070	0.39	0.66	0.24	0.37	1.04	0.41	0.39
Adipose Tissue Bl. Flow (l/min)	0.18	0.069	0.39	0.56	0.23	0.42	0.98	0.40	0.41
Yellow Marrow Bl. Flow (l/min)	0.0069	0.0022	0.32	0.10	0.017	0.16	0.068	0.012	0.18

Comparison of Organ and Tissue Volumes from P³M and Reference Values

	P³M			Fis.-Berg. 1983	CAPKR		ICRP (2001)		
Weight (kg) Vol (l)	Children(4-6)	Adult Males (25-35)	Adult Females (25-35)	Adult Males	Adult Males	Adult Females	Child 5 years	Adult Males	Adult Females
Weight	19	80	69	70	73	60	19	73	60
Red Marrow	0.43	1.52	1.02	0.062	-	-	0.33	1.13	0.87
Lungs	0.24	0.98	0.86	0.58	0.47	0.37	0.55	1.73	1.35
Brain	1.4	1.3	1.2	1.4	1.4	1.2	1.2	1.39	1.25
Kidneys	0.095	0.30	0.26	0.29	0.31	0.28	0.11	0.3	0.26
Liver	0.50	1.5	1.4	0.58	1.8	1.4	0.55	1.73	1.35
Pancreas	0.034	0.096	0.086	-	0.1	0.085	0.03	0.1	0.08
Thyroid	0.0053	0.019	0.018	0.027	-	-	0.01	0.02	0.017
Spleen	0.069	0.21	0.19	0.14	0.18	0.15	0.048	0.17	0.14
GI Organs	0.28	1.2	1.2	-	1.2	1.1	0.29	1.16	1.09
Blood	1.5	5.7	4.1	5.3	5.6	4	1.42	5.4	4.08
Plasma	0.97	3.4	2.6	-	3.1	2.8	-	-	-
Blood Cell	0.49	2.3	1.4	-	2.5	1.2	-	-	-
Total Poorly Perf.	5.5	35	25	33	-	-	-	-	-
Dermis	0.52	3.6	3.2	-	2.5	1.8	0.51	2.9	2
Epidermis	0.06	0.16	0.14	-	0.1	0.09	-	-	-
Skeletal Muscle	4.8	30	21	30	30	18	5.4	28	17
Heart	0.11	0.35	0.30	0.29	0.33	0.27	0.082	0.32	0.24
Tongue	0.023	0.095	0.082	-	-	-	-	0.07	0.06
Total Fatty Tissues	7.3	31	35	11	-	-	4	19	21
Adipose Tissue	7.0	28	33	8.7	13	18	3.8	16	20
Yellow Marrow	0.23	3.3	2.3	2.4	-	-	0.17	2.7	2
Bone tissue	1.0	3.9	2.6	-	-	-	0.76	3	2.2

Data Gaps in the Models of Physiological Parameters

The project identified a number of gaps in the published literature for anthropometry-based models of organ volumes and mass. Future work on modeling intra-individual variation in organ size should seek to address the following issues:

1. Better models of adult organ volumes. If they are not correlated with age, gender, height or weight are they correlated to LBM? Are there significant correlations between organs?

2. Models for the volumes of the breast, GI and the urogenital organs.

3. Better models of adipose tissue in children.

4. Better models of brain volume in adults and children.

5. Additional modeling of body composition in children ages six months to three years. Existing studies tend to focus on either newborns or children aged three and above resulting in a data gap for this age range.

6. The relationship of CO to organ volumes needs to be better defined. What is the source of the remaining variance that is not predicted by age, height, LBM, and weight?

Future Modeling of Physiological Parameters

The majority of the publications are less than five years old. This reflects the rapid development of the field of modeling organ weights and volumes.

In addition, NHANES IV is currently under way this survey includes whole body DXA assessment that will report TBBM, adipose tissue, and LBM for each individual.

Because of the ongoing publications and the NHANES IV data, the estimates of the parameters developed in this project should be revaluated in the near future.

Conclusions

The project successfully developed a tool for modeling autocorrelation between parameters typically used in PBPK modeling. While there is room for future improvements of the tool, the database and the software provide a useful tool for modeling variation in physiological parameters across individuals of different ages, genders and ethnicities.

References

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P³M can be downloaded from:

http://www.thelifelinegroup.org

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