Latent bone modelling for estimation of plutonium concentration in skeleton of former nuclear workers

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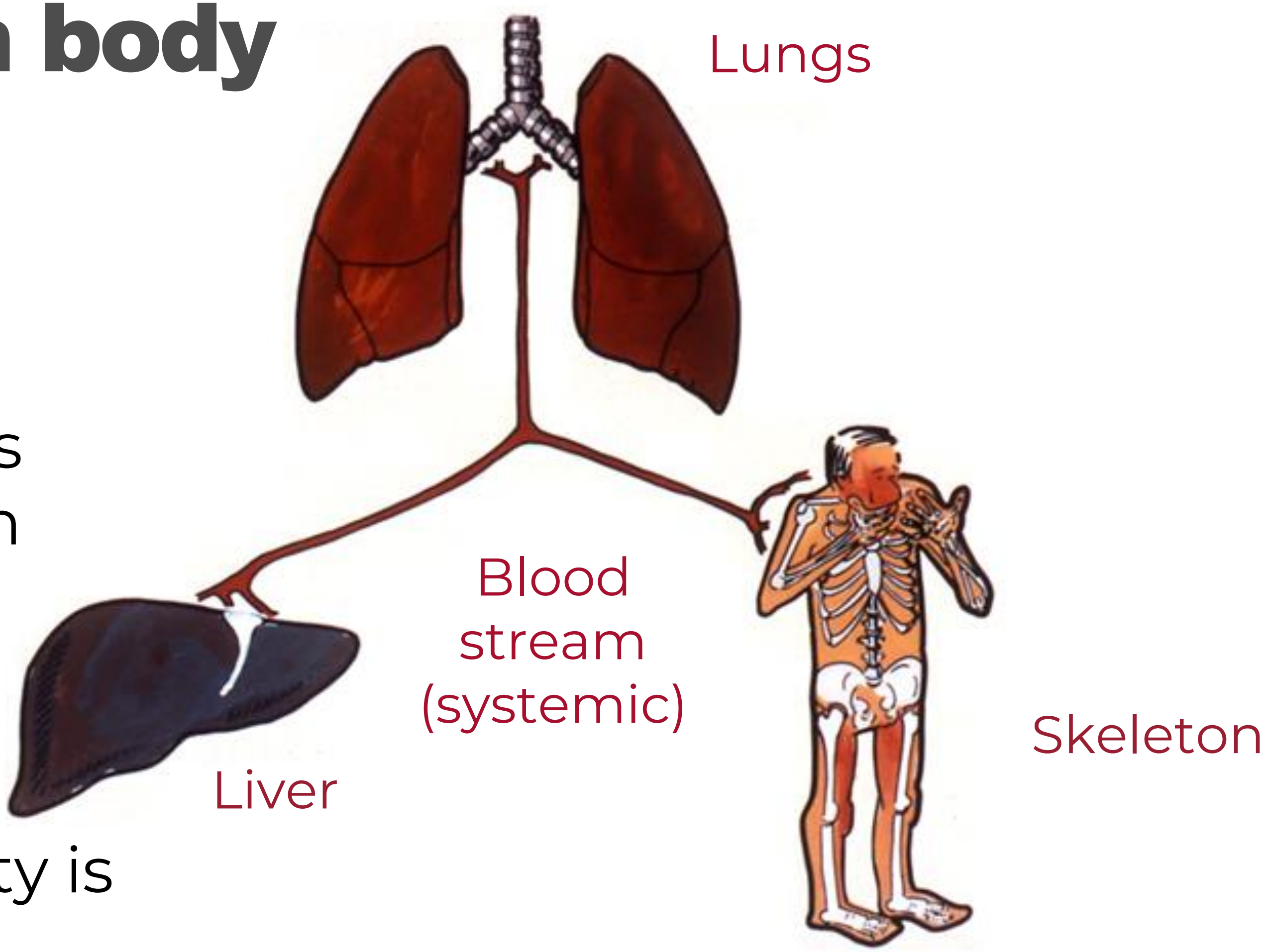
Plutonium in human body

- Skeleton and liver are major depository sites
- Estimation of activity in liver is straightforward – single organ
- Unlike for the skeleton which consists of 206 bones

$$A = C_{\text{skel}} \times \text{mass}$$

- Uncertainty in skeleton activity is higher



Simplified pathways for plutonium

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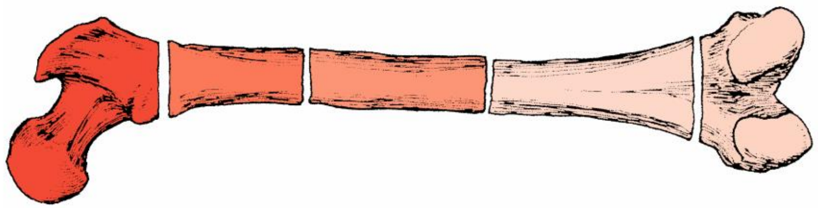
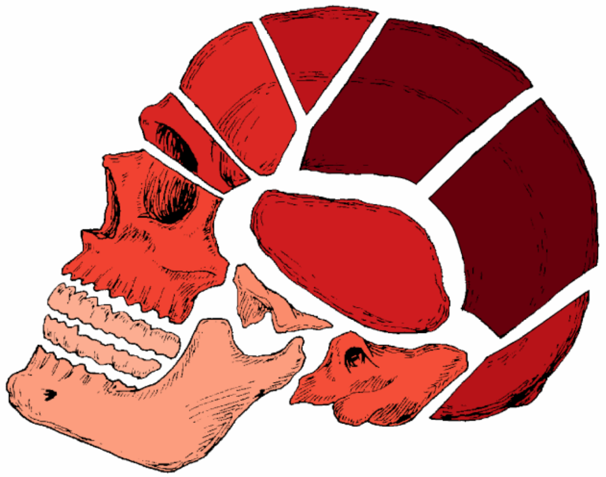
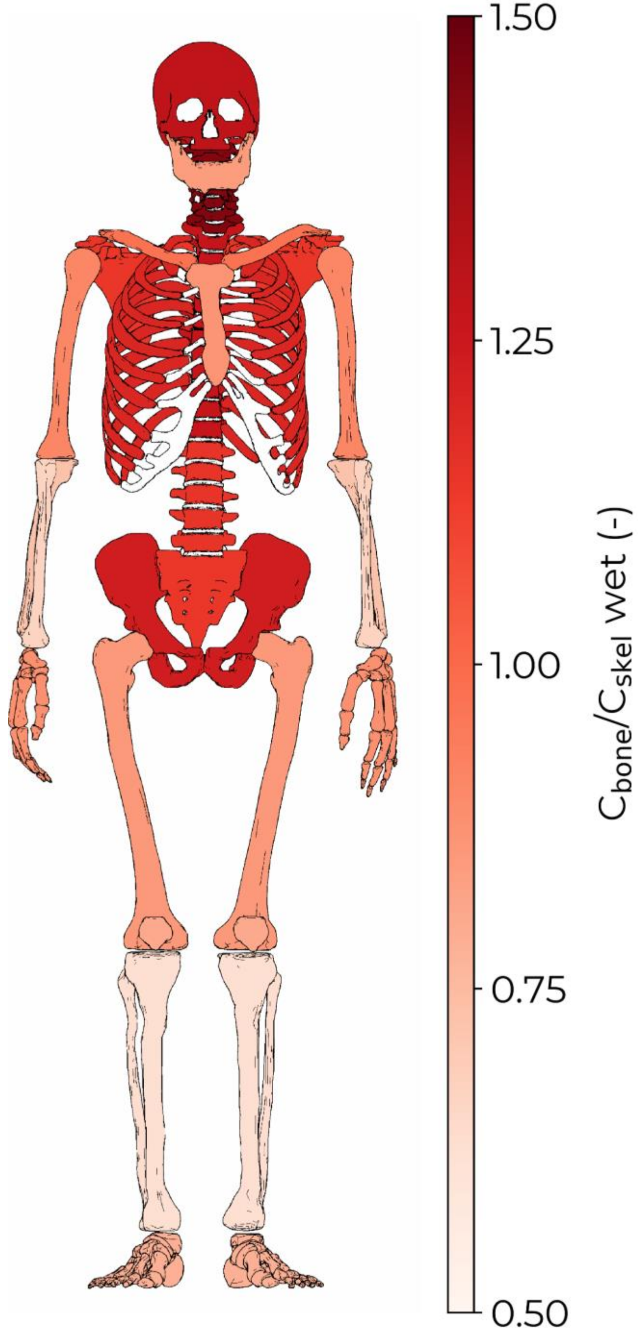
Non-uniform distribution of plutonium in skeleton

- Bones differ in plutonium concentration
- Bone parts differ in plutonium concentration
- How to estimate activity concentration in the skeleton C_{skel} from limited number of samples?







Examples of bone sample collection

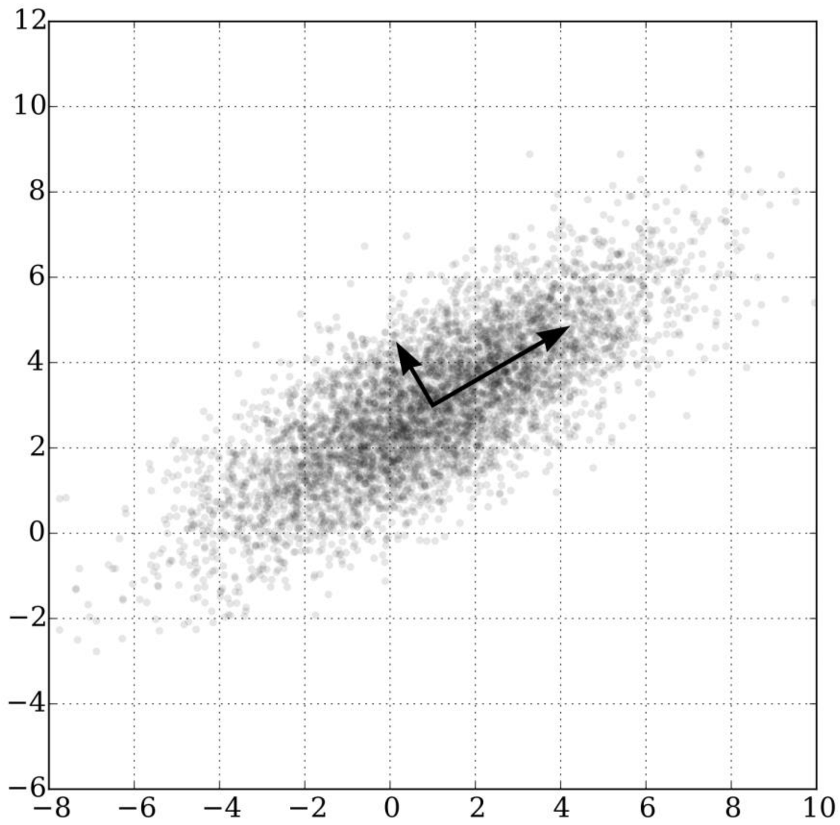
Case	Number of bone samples	^{239}Pu activity concentration in bone sample (Bq kg^{-1})											
		Parietal 1	Vert T7 arch	Vert T7 body	Clavicle SE	Clavicle shaft	Clavicle AE	Rib 7	Sternum	Hand and wrist	Femur MS	Femur DE	Patella
0719	4				14.1±0.9	18.9±0.6	16.0±0.8						22.4±0.4
0745	4									18.3±0.7	35.2±1.4	23.2±0.8	17.5±0.6
0778	4			87.5±3.1				85.0±2.0	34.7±1.1				125±4
0060	5	23.1±1.6		7.2±0.2				8.4±0.2	7.0±0.2		5.2±0.1		
0255	7			4.4±0.2	2.5±0.2	1.0±0.2	4.6±0.4	1.8±0.1	2.4±0.1				4.3±0.7
0631	7		22.9±1.0	12.9±0.5				18.9±0.8	12.0±0.4		12.3±0.5	10.5±0.4	12.2±0.5
0634	8	30.7±1.1	26.9±0.9	21.8±0.7				13.2±0.5	14.4±0.5		18.0±0.7	17.8±0.6	23.7±0.8

How to estimate C_{skel}

1. Average the bone samples concentrations
2. Weighted average of the measured bone sample concentrations
3. Multiple linear regression using whole body data – collinearity problems, sample size, imprecise and unstable estimates
4. Latent bone modelling (LBM) – principal component regression (Zhou et al. Health Phys. 122(4): S71-S72; 2022)

LBM: principal component analysis

- Principal components – orthogonal unit vectors (directions)
- 1st principal component maximises the variance
- 2nd maximises the variance while being orthogonal to the first, …
- Can be used to **reduce dimensionality** of the data and **preserve maximum information**
- New variables = **latent bones** are a linear combination of old variables

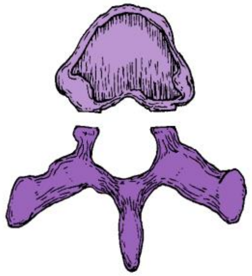
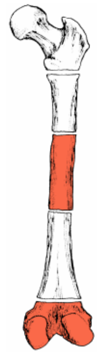
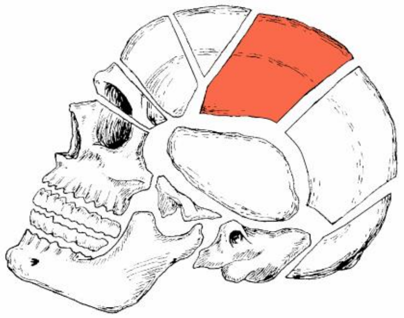


https://en.wikipedia.org/wiki/Principal_component_analysis#/media/File:GaussianScatterPCA.svg

LBM: principal component regression

- Principal component analysis – transform the bone sample concentrations to new latent bone variables
- Linear or multiple linear regression on transformed latent variables
- For this study LBM=PCR
- Implemented in Python 3.9, tested with GraphPad Prism 9

Data

- **Training dataset** with ‘known’ C_{skel}: 13 non-osteoporotic whole-body cases with half size of skeleton analysed
- **Studied cases** with ‘unknown’ C_{skel} **:** 7 cases with limited number of bones analysed (4 – 8)
  - ✓ Clavicle sternal end, clavicle shaft, and clavicle acromial end, patella
  - ✓ Hand and wrist, femur middle shaft, femur distal end, patella
  - ✓ **T7 vertebral body, rib 7, sternum, patella**
  - ✓ T7 vertebral body, femur middle shaft, skull parietal 1, rib 7, sternum
  - ✓ Patella, T7 vertebral body, rib 7, sternum, clavicle sternal end, clavicle shaft, clavicle acromial end
  - ✓ T7 vertebral arch, T7 vertebral body, rib 7, sternum, femur middle shaft, femur distal end, patella
  - ✓ Skull parietal 1, T7 vertebral arch, T7 vertebral body, rib 7, sternum, femur middle shaft, femur distal end, patella

Training data: standardization

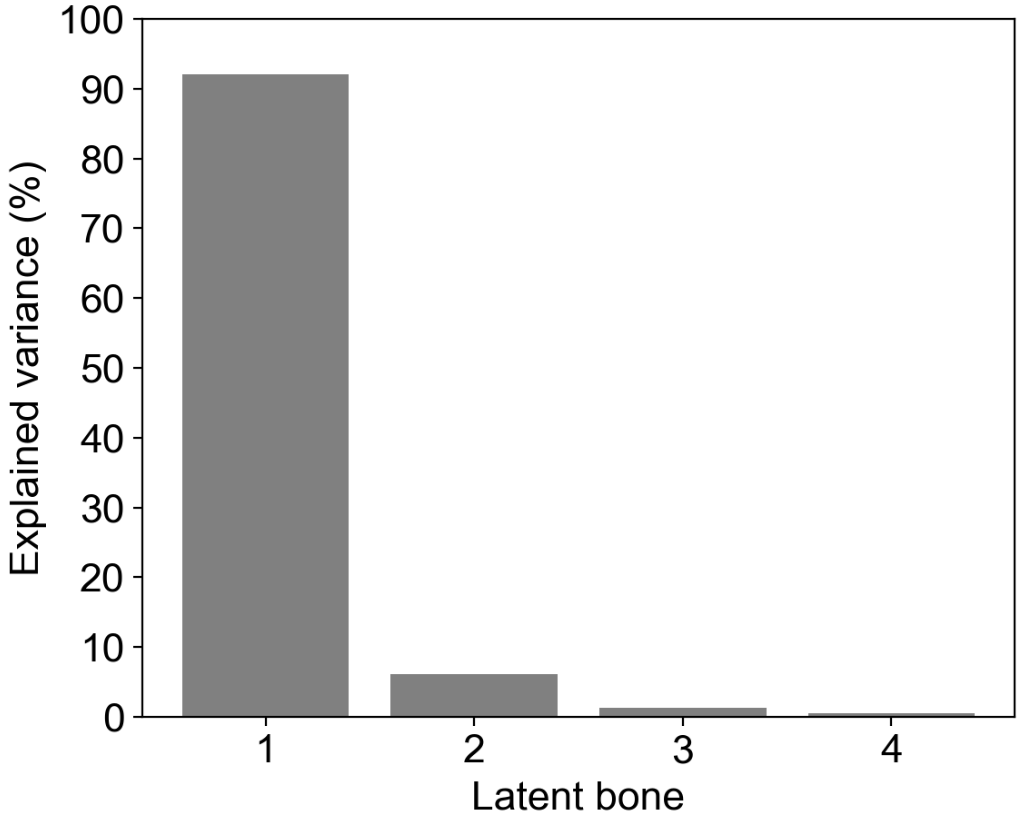
$$S_{\text{bone},i} = \frac{C_{\text{bone},i} - \text{Mean}_{\text{bone}}}{\text{SD}_{\text{bone}}}$$

	Measured concentration (Bq/kg)			
Case	T7 Body	Rib 7	Sternum	Patella
1	4.9	6.5	4.7	5.3
2	18.9	13.9	5.6	8.8
3	13.9	14.3	10.5	6.1
4	20.5	24.8	17.1	14.3
5	53.1	58.8	44.8	34.4
6	17.1	15.8	16.1	7.1
7	3.2	2.6	2.9	2.9
8	1.6	2.3	1.1	1.7
9	4.9	5.2	3.2	1.6
10	35.1	26.0	22.9	39.8
11	38.0	36.6	31.6	18.8
12	8.1	5.8	7.1	6.4
13	7.3	19.7	7.9	16.1
Mean	17.4	17.9	13.5	12.6
SD	15.8	16.0	12.9	12.2

	Standardized (-)			
Case	T7 Body	Rib 7	Sternum	Patella
1	-0.8	-0.7	-0.7	-0.6
2	0.1	-0.3	-0.6	-0.3
3	-0.2	-0.2	-0.2	-0.5
4	0.2	0.4	0.3	0.1
5	2.3	2.6	2.4	1.8
6	0.0	-0.1	0.2	-0.5
7	-0.9	-1.0	-0.8	-0.8
8	-1.0	-1.0	-1.0	-0.9
9	-0.8	-0.8	-0.8	-0.9
10	1.1	0.5	0.7	2.2
11	1.3	1.2	1.4	0.5
12	-0.6	-0.8	-0.5	-0.5
13	-0.6	0.1	-0.4	0.3
Mean	0	0	0	0
SD	1	1	1	1

Principal component regression T7 body, Rib 7, Sternum, Patella

- Mathematically: finding eigenvalues of data correlation matrix
- L_1 explains 92% of variance of the training set
- $L_1 = 0.512\, S_{\mathrm{T7\ body}} + 0.507\, S_{\mathrm{Rib\ 7}} + 0.509\, S_{\mathrm{Sternum}} + 0.470\, S_{\mathrm{Patella}}$
- $C_{\mathrm{skel}} = a_0 + a_1 L_1 + \cdots + a_n L_n$
- $C_{\mathrm{skel}} = a_0 + a_1 L_1$



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Prediction of C_{skel}

- $$L_{1,i} = 0.512\,\frac{c_{\text{T7body},i} - \text{Mean}_{\text{T7body}}}{\text{SD}_{\text{T7body}}} + 0.507\,\frac{c_{\text{Rib7},i} - \text{Mean}_{\text{Rib7}}}{\text{SD}_{\text{Rib7}}} + 0.509\,\frac{c_{\text{Sternum},i} - \text{Mean}_{\text{Sternum}}}{\text{SD}_{\text{Sternum}}} + 0.470\,\frac{c_{\text{Patella},i} - \text{Mean}_{\text{Patella}}}{\text{SD}_{\text{Patella}}}$$

$$C_{\text{skel},i} = a_0 + a_1 L_{1,i}$$

$$C_{\text{skel}} = 1.275 + 0.198\ C_{\text{T7body}} + 0.193\ C_{\text{Rib 7}} + 0.240\ C_{\text{Sternum}} + 0.236\ C_{\text{Patella}}$$

- $\text{Mean}_{\text{bone}}$ and SD_{bone} are constants depending on the training set

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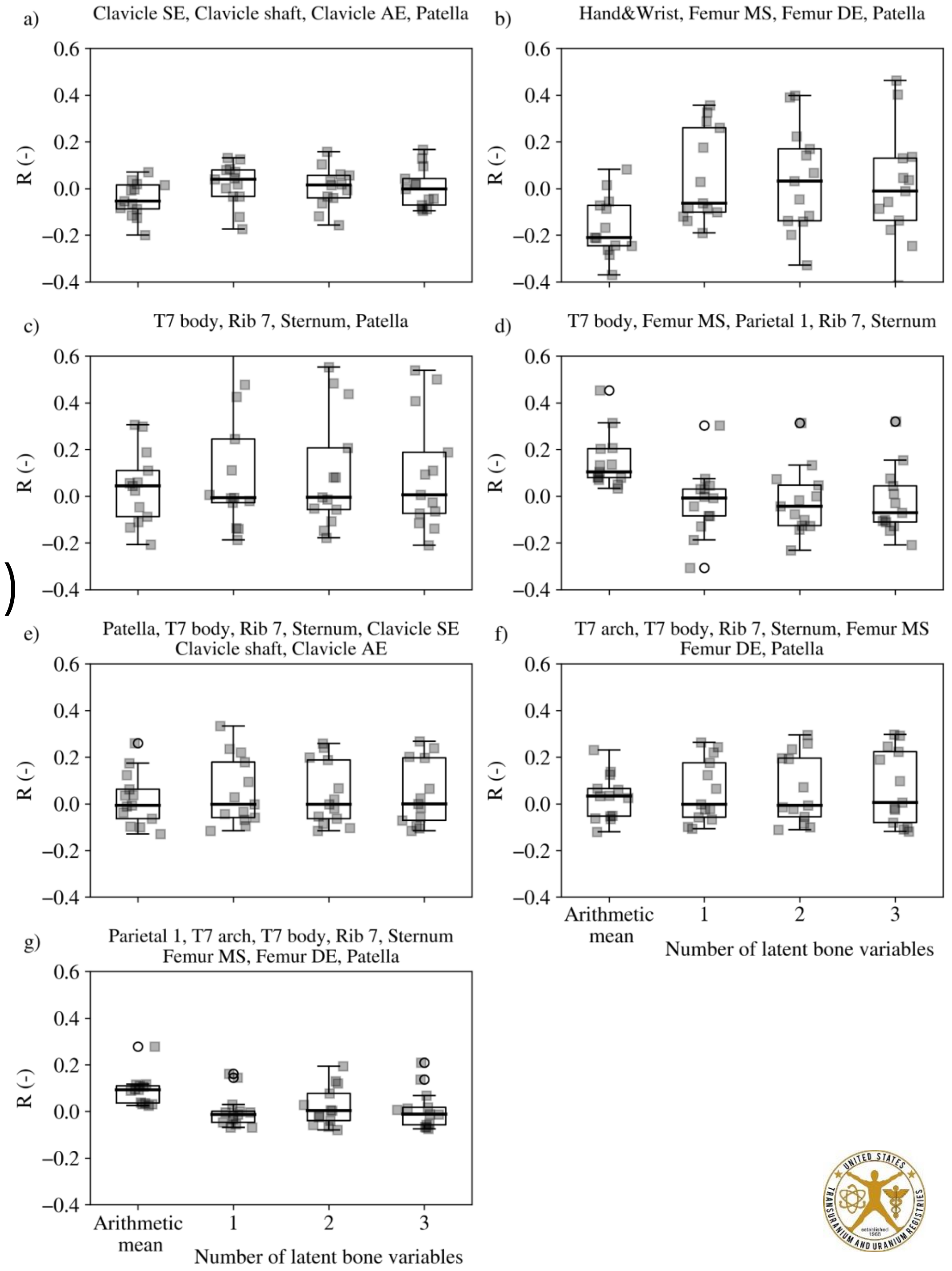
Estimated C_{skel}

- Each case is a separate latent bone model (different bone samples available)
- Mean and LBM within 20%
- Good agreement if the set of bone samples represent C_{skel}
- Lower error than the mean

Case	C_{skel} (Bq kg^{-1})		LBM vs Mean (%)
	Mean	LBM	
0719	17.9±1.8	18.4±0.4	-3
0745	23.6±4.1	29.0±1.3	-19
0778	83.2±18.6	72.9±2.3	14
0060	10.2±3.3	8.6±0.4	19
0255	3.0±0.5	3.4±0.5	-12
0631	14.5±1.7	14.0±0.3	4
0634	20.8±2.2	19.9±0.3	5

Leave-one-out cross validation

- Box-plots arithmetic mean vs LBM
- On average similar median estimates, except for two sets: b(21%) and d(10%)
- Mean accuracy depends on bone samples – no guarantee
- One latent variable is enough
- Individual variability is high



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Implementation of LBM

- Development of C_{skel} calculator

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SECTION TITLE HERE

LATENT BONE MODELLING FOR ESTIMATION OF PLUTONIUM CONCENTRATION IN SKELETON OF FORMER NUCLEAR WORKERS

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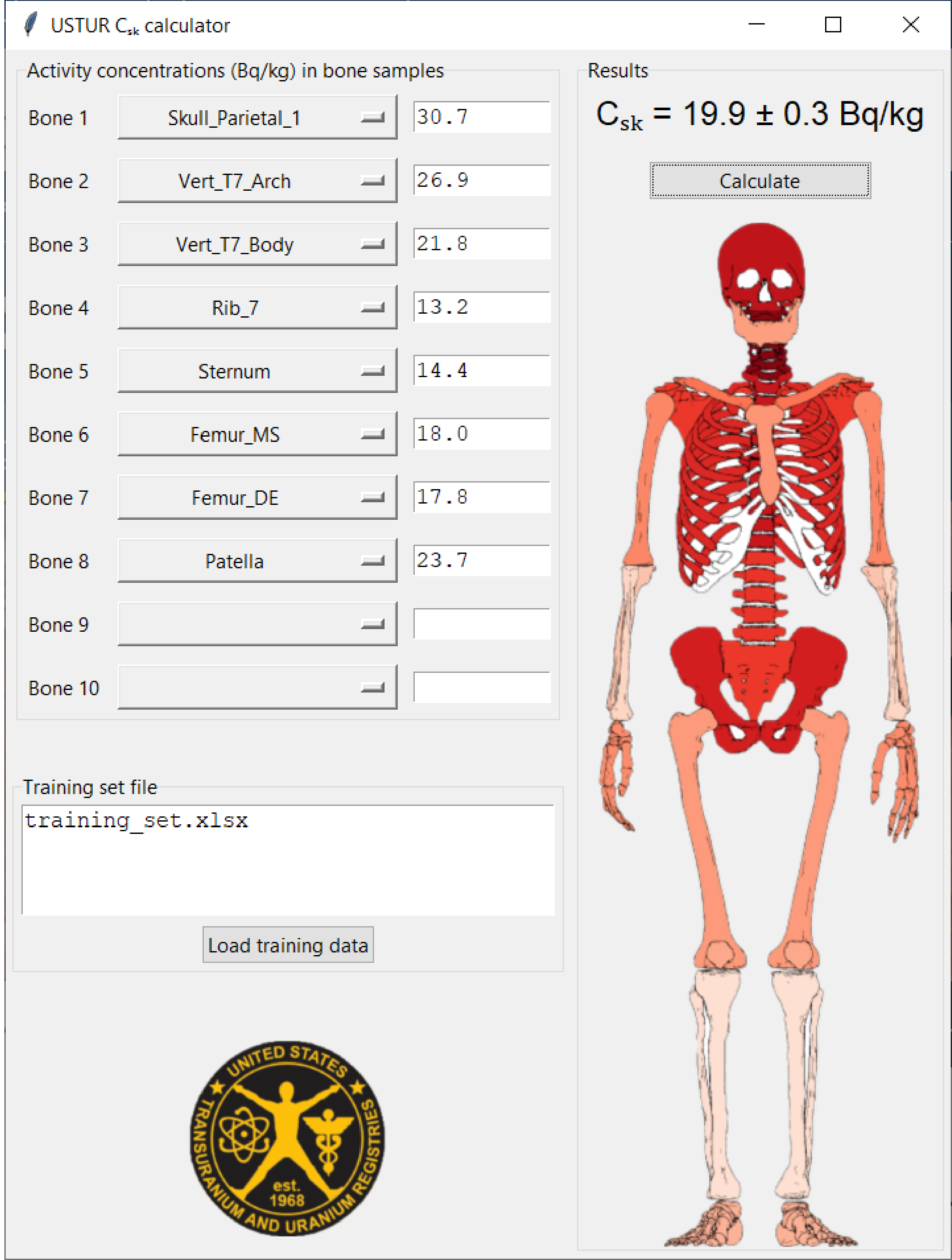
The skeleton is a major plutonium retention site in the human body. The estimation of the total plutonium activity in the skeleton is a challenging problem. For most tissue donors at the United States Transuranium and Uranium Registries, a limited number of bone samples is available. The skeleton activity is calculated using plutonium activity concentration (C_{skel}) and skeleton weight. If limited number of bone samples was analysed, C_{skel} must be estimated. Data of 13 non-osteoporotic whole-body donors were used for principal component regression (PCR) and the results were used to estimate C_{skel} for seven cases with four to eight analysed bone samples. PCR was compared to arithmetic mean estimate. This analysis suggests that PCR offers significant reduction of uncertainty of C_{skel} estimate for the studied cases.



Conclusions

- Latent bone modeling method for C_{skel} estimate was demonstrated and compared to arithmetic mean estimates
- For 7 cases, LBM/PCR offers similar central estimates of C_{skel}
- LBM/PCR is a preferred method
  - ✓ lower risk of bias for non-representative bone sampling
  - ✓ utilizes all available information
  - ✓ reduction of uncertainty by a factor of 4.7 (for studied 7 sets)

Thank you for your attention