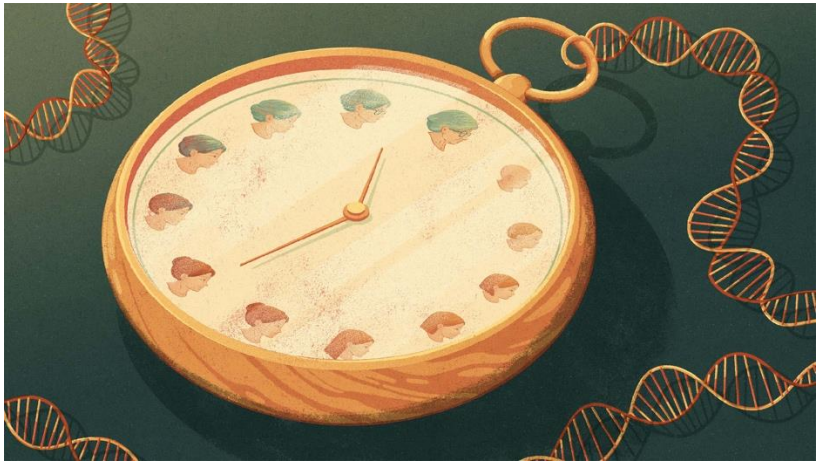
Leveraging Deep Learning with toRch for Next-Generation Epigenetic Clocks

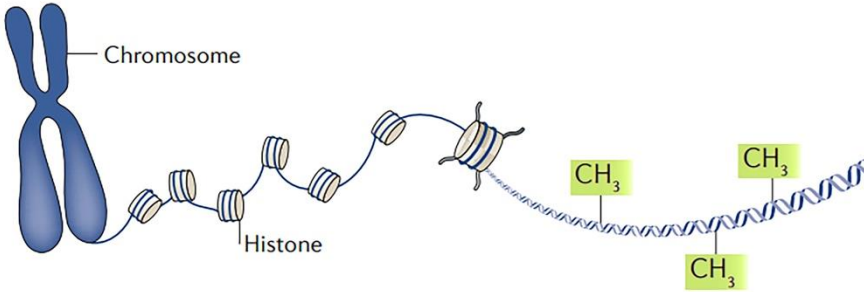


github.com/BacZemin

2025-06-24

Jamie Park (PhD candidate at VAI)

The first epigenetic clock based on DNA methylation



Using Machine learning, Methylomes can predict chronological age.

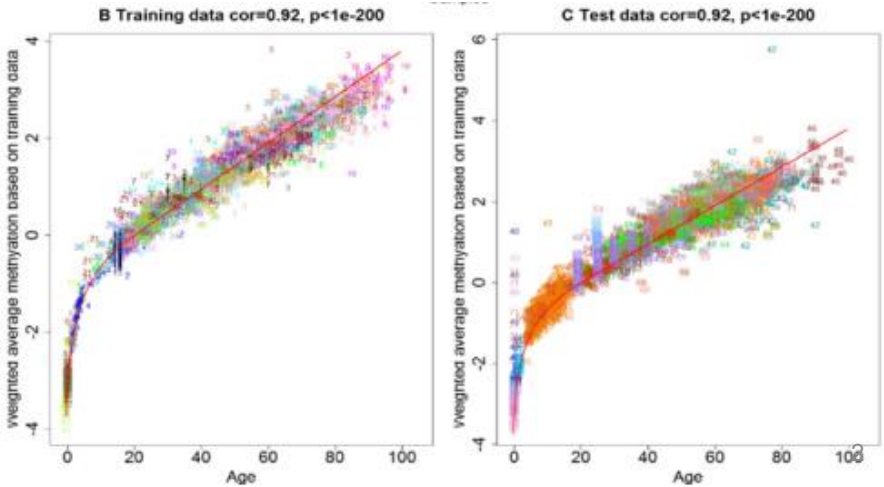
Horvath *Genome Biology*, **14**:R115
http://genomebiology.com//14/10/R115

Genome Biology

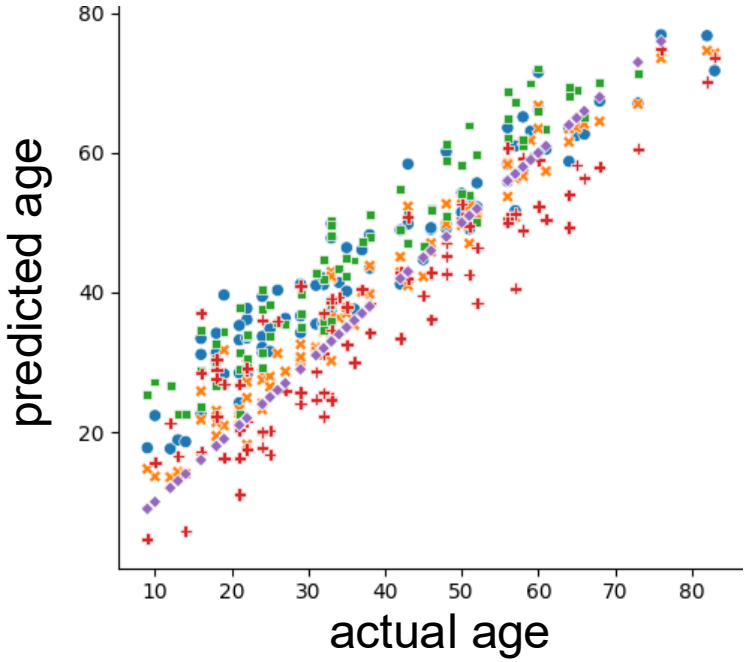
RESEARCH Open Access

DNA methylation age of human tissues and cell types

Steve Horvath[1,2,3]



The big 3 epigenetic clocks



Clock	MAE (years)	Pearson's r
Horvath Clock v1	7.4751	0.9510
Horvath Clock v2	3.1560	0.9791
Hannum Clock	8.8177	0.9679
PhenoAge Clock	6.2097	0.9158

why `elastic net` is useful for DNA methylation clocks

nature reviews genetics https://doi.org/10.1038/s41576-024-00807-w

Review article Check for updates

Epigenetic ageing clocks: statistical methods and emerging computational challenges

Andrew E. Teschendorff[1] & Steve Horvath[2]

Table 1 | DNA methylation clocks for humans

Name	Tissue	Programme	Method
Chronological age clocks			
Horvath	Multi-tissue	R	Elastic net
Hannum	Whole blood	R	Elastic net
PCHorvath1/2 PCHannum	Multi-tissue, whole blood	R	PC-based regression
Zhang	Whole blood	R	Elastic net
SkinBlood	Skin, whole blood	R	Elastic net
AltumAge	Multi-tissue	Python	Deep neural net
IntrinClock	Multi-tissue	R	Elastic net
MEAT	Skeletal muscle	R	Elastic net
Cortical clock	Brain cortex	R	Elastic net
PedBE	Buccal swabs	R	Elastic net

- elastic net is Ridge (L2) + Lasso (L1)
- these are ‘regularization’ ML methods to improve prediction.

- Usually, there’s WAY more probes (850k) than we have samples.
- Fitting a line when # parameters > # sample size doesn’t work.
- To fix this, we can add penalization (lambda) to each parameter

Ridge Lasso

$$\hat{\beta} \equiv \underset{\beta}{\operatorname{argmin}}(\|y - X\beta\|^2 + \lambda_2 \|\beta\|^2 + \lambda_1 \|\beta\|_1).$$

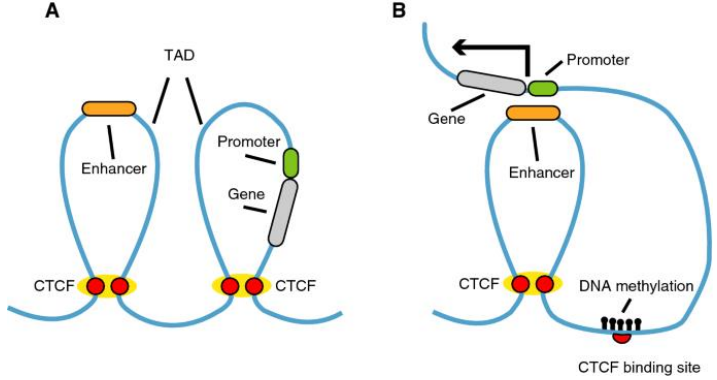
but elastic net has limits

- 1. Linearity Assumption

biological ageing is probably not that simple

- 2. Ignores Interaction between CpG

genome is a set of tangled strings in 3D



- 3. multicollinearity based feature selection

Lasso results in random selection of similar behaving probes


Article

https://doi.org/10.1038/s41467-024-47316-2

Nonlinear DNA methylation trajectories in aging male mice

Received: 10 July 2023

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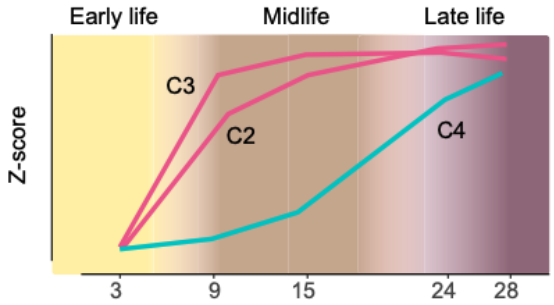
Maja Olecka[1,5], Alena van Bömmel[1,5], Lena Best[2], Madlen Haase[3], Silke Foerste[1], Konstantin Riege[1], Thomas Dost[2], Stefano Flor[2], Otto W. Witte[3], Sören Franzenburg[4], Marco Groth[1], Björn von Eyss[1], Christoph Kaleta[2,6], Christiane Frahm[3,6] & Steve Hoffmann[1,6]



Recent advent of ‘deep-learning epigenetic clocks’

npj | aging

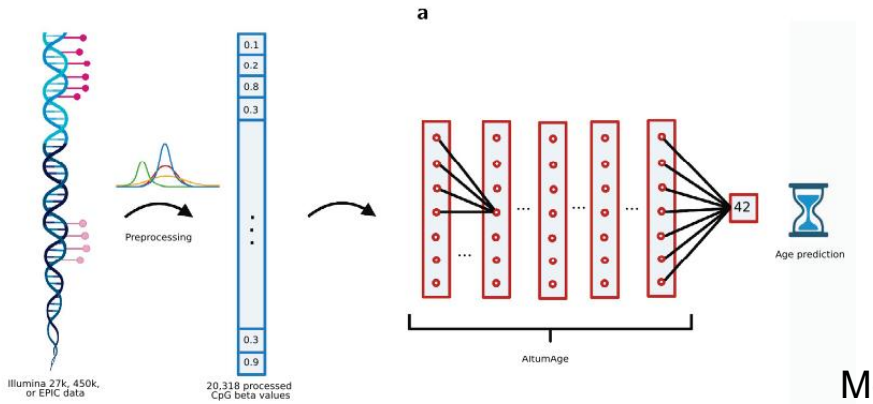
www.nature.com/npjamd

ARTICLE OPEN

Check for updates

A pan-tissue DNA-methylation epigenetic clock based on deep learning

Lucas Paulo de Lima Camillo[1], Louis R. Lapierre[2] and Ritambhara Singh[1,3]

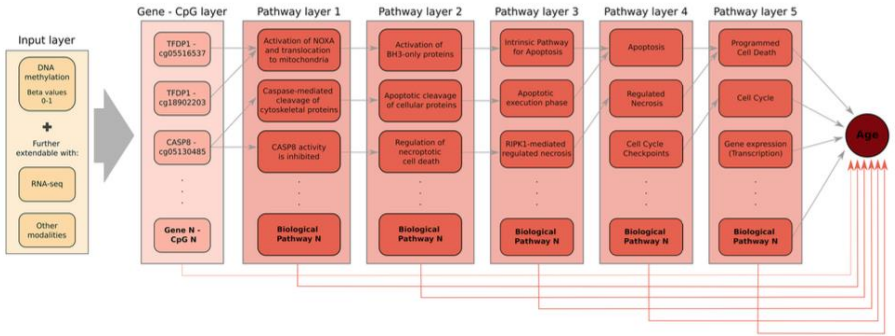


Check for updates

OPEN

Biologically informed deep learning for explainable epigenetic clocks

Aurel Prosz[1], Orsolya Pipek[2], Judit Börcsök[1,3], Gergely Palla[4,5], Zoltan Szallasi[1], Sandor Spisak[6] & István Csabai[2]



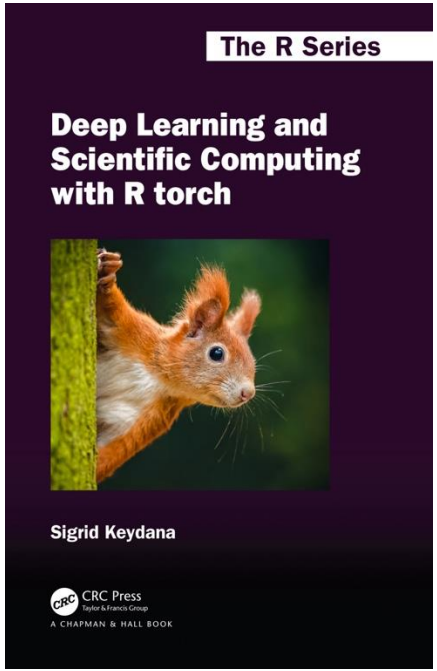
Most of these pipelines utilize `pytorch` or `tensorflow`

using torch; R interface to PyTorch

```{r check if torch is online}
library(torch)

# --- Device Configuration ---
if (cuda_is_available()) {
  device <- torch_device("cuda")
  current_gpu_index <- cuda_current_device() # Get the index of the active GPU
  num_gpus <- cuda_device_count()           # Get the total number of GPUs available
  print(paste0("✅ CUDA (GPU) is available. Set device to 'cuda'."))
  print(paste0("   Currently active GPU index: ", current_gpu_index))
  print(paste0("   Total CUDA devices found: ", num_gpus))
} else {
  device <- torch_device("cpu")
  print("⚠️ CUDA (GPU) not found. Using device: CPU")
}

seed <- 42
set.seed(seed)
torch::torch_manual_seed(seed)
```

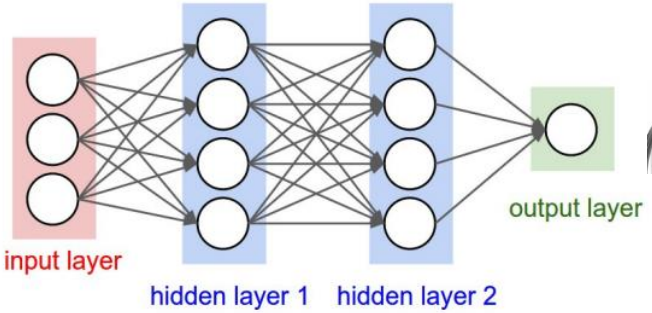


great tutorials by Sigrid Keydana
https://skeydan.github.io/Deep-Learning-and-Scientific-Computing-with-R-torch/

3-layer MLP architecture with GPU (4x NVIDIA L40S)

```{r define_mlp}
# --- Define the MLP Model ---
age_predictor_mlp <- nn_module(
  "AgePredictorMLP",
  initialize = function(input_size,
                        hidden1_size = 512,
                        hidden2_size = 256,
                        dropout_rate = 0.4) {
    self$network <- nn_sequential(
      # Layer 1
      nn_linear(input_size, hidden1_size),
      nn_batch_norm1d(hidden1_size),
      nn_relu(),
      nn_dropout(dropout_rate),
      # Layer 2
      nn_linear(hidden1_size, hidden2_size),
      nn_batch_norm1d(hidden2_size),
      nn_relu(),
      nn_dropout(dropout_rate),
      # Output Layer
      nn_linear(hidden2_size, 1)
    )
  },
  forward = function(x) {
    self$network(x)
  }
)

print("AgePredictorMLP nn_module defined.")
```



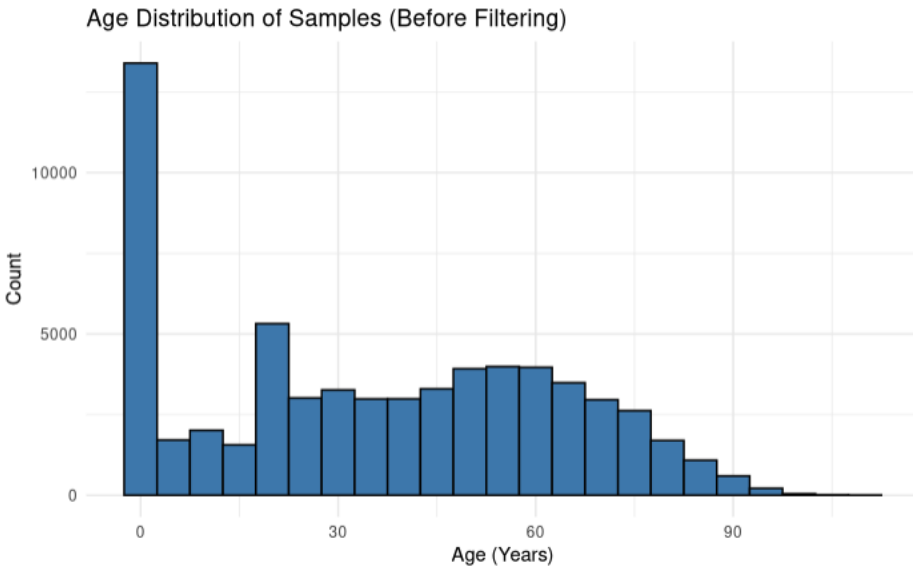

```{r}
# --- Training Hyperparameters ---
num_epochs <- 100
batch_size <- 128
learning_rate <- 1e-4
weight_decay <- 1e-5
patience <- 15
dropout_rate <- 0.4
split_ratios <- list(train = 0.70, val = 0.15, test = 0.15)
num_workers <- 0 # Set based on your system capabilities
```

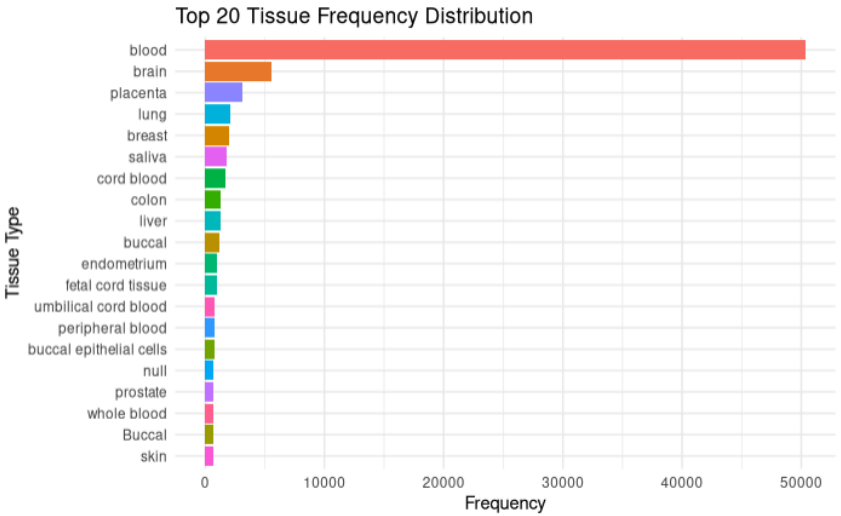
Training data: Illumina EPIC methylation microarrays from blood samples

- curated ~9000 EPIC array methylation data with metadata (age, sex, diseased)
- from the biomarkers of aging platform
  - https://bio-learn.github.io/

BIOMARKERS OF AGING CHALLENGE

BIOMARKERS OF AGING CONSORTIUM · Methuselah Foundation · VoLoFoundation





Main Training Loop

```{r}
results_summary <- list()

# Iterate through each defined probe set
for (probe_set_name in names(probe_sets_to_run)) {

  cat(paste0("\n--- Starting Experiment: ", probe_set_name, " ---\n"))

  # 1. DATA LOADING AND PREPROCESSING
  cat("1. Loading and preprocessing data...\n")
  X_full         <- py_to_r(np$load(beta_matrix_path))
  all_probe_ids  <- as.character(py_to_r(np$load(probe_ids_path,
allow_pickle=TRUE)))
  all_sample_ids <-
toupper(trimws(as.character(py_to_r(np$load(sample_ids_path,
allow_pickle=TRUE)))))
  meta_df        <- arrow::read_feather(metadata_path)

  # Align methylation data with metadata
  X_full         <- t(X_full)
  meta_dt        <- as.data.table(meta_df)[, .(gsm =
toupper(trimws(as.character(gsm))), age_years)]
  samples_dt     <- data.table(gsm = all_sample_ids, original_order =
1:length(all_sample_ids))
  meta_aligned   <- meta_dt[samples_dt, on = "gsm", nomatch=0]
[order(original_order)]
```

1. load and initialize the dataset.
   lightweight dataformat (feather, arrow or npy)
   record time point.

2. Prepare dataset
   train:validation:test = 70:15:15
   feature scaling (beta standardization)

3. Create `tensor`
   convert R matrices in to pytorch tensors

Main Training Loop

```
# 2. DATA SPLITTING & SCALING
cat("2. Splitting and scaling data...\n")
# Split data into training, validation, and test sets
split_obj      <- initial_split(data.frame(idx = 1:nrow(X_filtered)), prop =
split_ratios$train)
train_indices  <- training(split_obj)$idx
temp_indices   <- testing(split_obj)$idx
val_test_split <- initial_split(data.frame(idx = temp_indices), prop = split_ratios$val /
(split_ratios$val + split_ratios$test))
val_indices    <- training(val_test_split)$idx
test_indices   <- testing(val_test_split)$idx

# Scale features based on the training set
train_means    <- colMeans(X_filtered[train_indices, ], na.rm = TRUE)
train_sds      <- apply(X_filtered[train_indices, ], 2, sd, na.rm = TRUE)
train_sds[is.na(train_sds) | train_sds == 0] <- 1 # Avoid division by zero

X_train_scaled <- scale(X_filtered[train_indices, ], center = train_means, scale =
train_sds)
X_val_scaled   <- scale(X_filtered[val_indices, ], center = train_means, scale = train_sds)
X_test_scaled  <- scale(X_filtered[test_indices, ], center = train_means, scale = train_sds)

y_train <- ages[train_indices]; y_val <- ages[val_indices]; y_test <- ages[test_indices]
```

1. load and initialize the dataset.
   - lightweight dataformat (feather, arrow or npy)
   - record time point.

2. Prepare dataset
   - train:validation:test = 70:15:15
   - feature scaling (beta standardization)

3. Create `tensor`
   - convert R matrices in to pytorch tensors

Main Training Loop

```
# 3. DATALOADER CREATION
cat("3. Creating PyTorch dataloaders...\n")
train_dataset <- tensor_dataset(
  torch_tensor(X_train_scaled, dtype = torch_float32()),
  torch_tensor(y_train, dtype = torch_float32())$unsqueeze(2)
)
val_dataset <- tensor_dataset(
  torch_tensor(X_val_scaled, dtype = torch_float32()),
  torch_tensor(y_val, dtype = torch_float32())$unsqueeze(2)
)
test_dataset <- tensor_dataset(
  torch_tensor(X_test_scaled, dtype = torch_float32()),
  torch_tensor(y_test, dtype = torch_float32())$unsqueeze(2)
)

train_loader <- dataloader(train_dataset, batch_size = batch_size, shuffle = TRUE,
num_workers = num_workers)
val_loader   <- dataloader(val_dataset, batch_size = batch_size, shuffle = FALSE,
num_workers = num_workers)
test_loader  <- dataloader(test_dataset, batch_size = batch_size, shuffle = FALSE,
num_workers = num_workers)
```

1. load and initialize the dataset.
   lightweight dataformat (feather, arrow or npy)
   record time point.

2. Prepare dataset
   train:validation:test = 70:15:15
   feature scaling (beta standardization)

3. Create `tensor`
   convert R matrices in to pytorch tensors

Main Training Loop

```r
# 4. MODEL INITIALIZATION AND TRAINING
cat("4. Initializing and training the model...\n")
model <- age_predictor_mlp(input_size = n_features, dropout_rate = dropout_rate)$to(device = device)
optimizer <- optim_adamw(model$parameters, lr = learning_rate, weight_decay = weight_decay)
scheduler <- lr_reduce_on_plateau(optimizer, patience = 5, factor = 0.2)

best_val_loss <- Inf
epochs_no_improve <- 0
history <- data.frame()

for (epoch in 1:num_epochs) {
  # Training phase
  model$train()
  train_loss <- 0
  coro::loop(for (b in train_loader) {
    optimizer$zero_grad()
    outputs <- model(b[[1]]$to(device = device))
    loss <- nnf_smooth_l1_loss(outputs, b[[2]]$to(device = device))
    loss$backward()
    optimizer$step()
    train_loss <- train_loss + loss$item()
  })

  # Validation phase
  model$eval()
  val_loss <- 0
  all_preds <- c(); all_labels <- c()
  with_no_grad({
    coro::loop(for (b in val_loader) {
      outputs <- model(b[[1]]$to(device = device))
      loss <- nnf_smooth_l1_loss(outputs, b[[2]]$to(device = device))
      val_loss <- val_loss + loss$item()
      all_preds <- c(all_preds, as.numeric(outputs$cpu()))
      all_labels <- c(all_labels, as.numeric(b[[2]]$cpu()))
    })
  })
```

4. Actual train the model

   Training phase

   Validation phase

```
--- Starting Experiment: all_probes ---
1. Loading and preprocessing data...
  Prepared data with 437810 features.
2. Splitting and scaling data...
3. Creating PyTorch dataloaders...
4. Initializing and training the model...
  Epoch 01: Val Loss: 35.9808, Val MAE: 35.8958
  Epoch 02: Val Loss: 35.4621, Val MAE: 35.3992
  Epoch 03: Val Loss: 34.9516, Val MAE: 34.9020
  Epoch 04: Val Loss: 34.3778, Val MAE: 34.3547
  Epoch 05: Val Loss: 33.7785, Val MAE: 33.7739
  Epoch 06: Val Loss: 33.3495, Val MAE: 33.3548
```

~45 min

```
  Epoch 97: Val Loss: 2.0099, Val MAE: 2.4054
  Epoch 98: Val Loss: 2.0611, Val MAE: 2.4506
  Epoch 99: Val Loss: 1.9592, Val MAE: 2.3639
  Epoch 100: Val Loss: 2.0218, Val MAE: 2.4205
```

5. try the best model on test set and save

Main Training Loop

```r
# 5. FINAL EVALUATION ON TEST SET
cat("5. Evaluating on the test set...\n")
# Load best model and evaluate
best_model <- age_predictor_mlp(input_size = n_features, dropout_rate = dropout_rate)
best_model$load_state_dict(torch_load("best_model.pt"))
best_model$to(device = device)$eval()

test_preds <- c()
with_no_grad({
  coro::loop(for (b in test_loader) {
    outputs <- best_model(b[[1]]$to(device = device))
    test_preds <- c(test_preds, as.numeric(outputs$cpu()))
  })
})
test_preds_corr <- pmax(0, test_preds)

final_mae <- mae_vec(truth = y_test, estimate = test_preds_corr)
final_rsq <- rsq_vec(truth = y_test, estimate = test_preds_corr)
```

4. Actual train the model

   Training phase

   Validation phase

```
--- Starting Experiment: all_probes ---
1. Loading and preprocessing data...
  Prepared data with 437810 features.
2. Splitting and scaling data...
3. Creating PyTorch dataloaders...
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  Epoch 01: Val Loss: 35.9808, Val MAE: 35.8958
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  Epoch 04: Val Loss: 34.3778, Val MAE: 34.3547
  Epoch 05: Val Loss: 33.7785, Val MAE: 33.7739
  Epoch 06: Val Loss: 33.3495, Val MAE: 33.3548
```
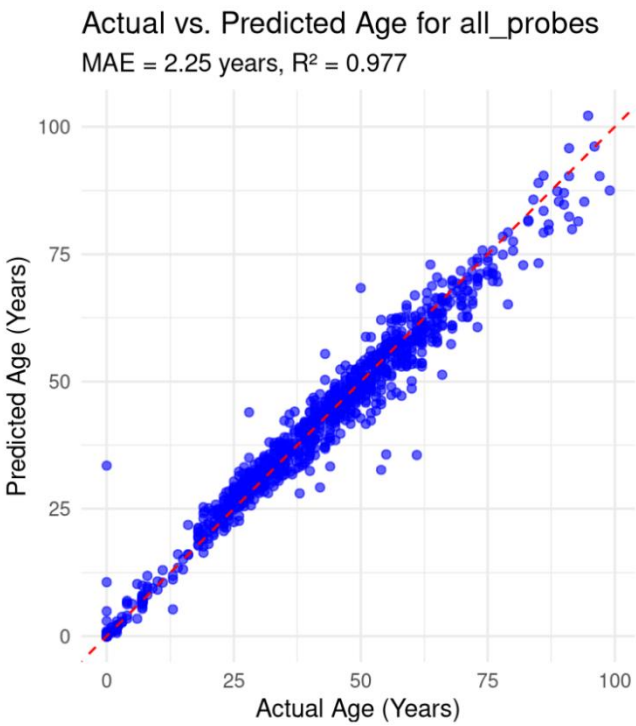
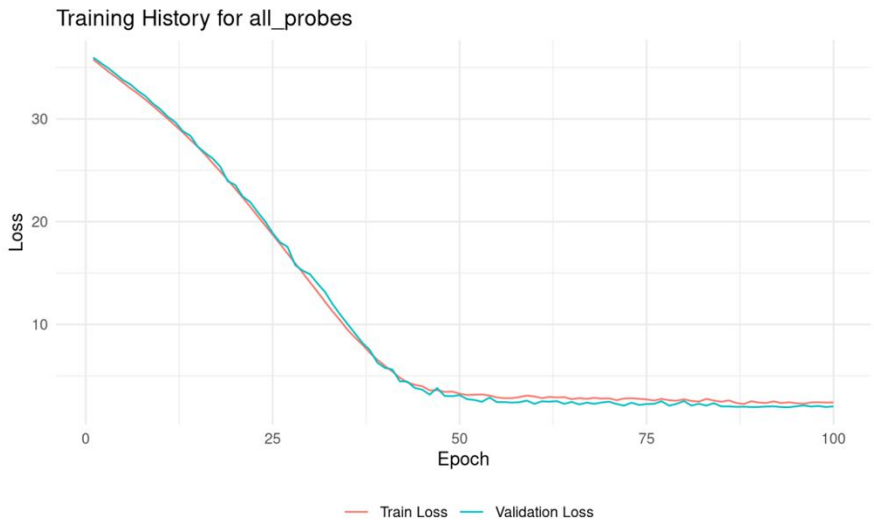

~45 min

```
Epoch 97: Val Loss: 2.0099, Val MAE: 2.4054
Epoch 98: Val Loss: 2.0611, Val MAE: 2.4506
Epoch 99: Val Loss: 1.9592, Val MAE: 2.3639
Epoch 100: Val Loss: 2.0218, Val MAE: 2.4205
```

5. try the best model on test set and save

Results (using all-probe set)





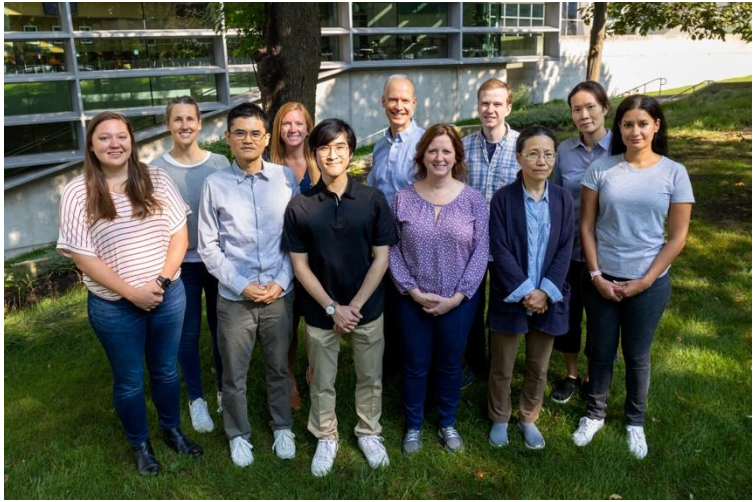
Testing set shows a very well trained model

MAE = 2.25, R^2 = 0.977

tl;dr

- R-torch can be a powerful tool for deep learning.
- deep-learned epigenetic clocks can predict age more accurately than elastic net clocks.

Acknowledgements



Laird Lab
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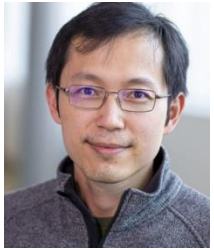

Special Thanks

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VAN ANDEL INSTITUTE®

NIH National Institute on Aging

github.com/BacZemin

check my knitted qmd at github!