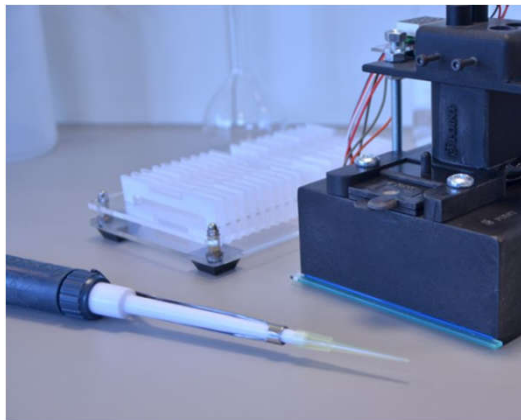


F-POINT ALGORITHM

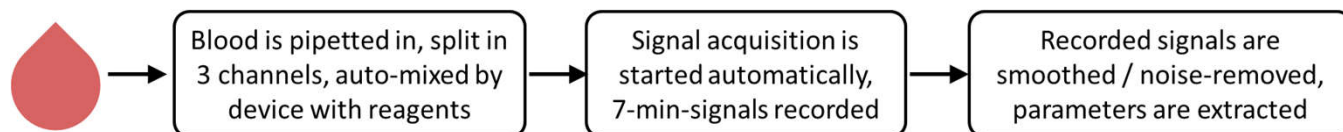
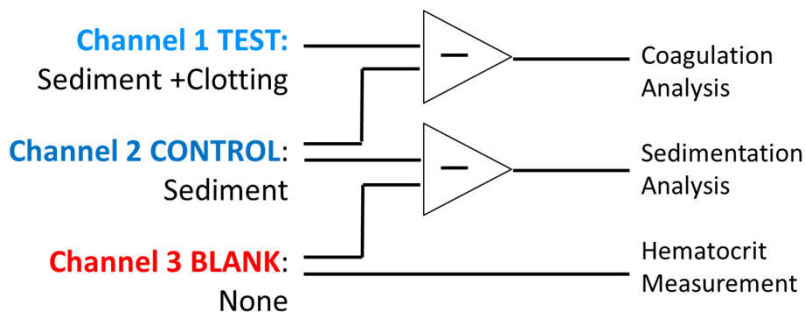
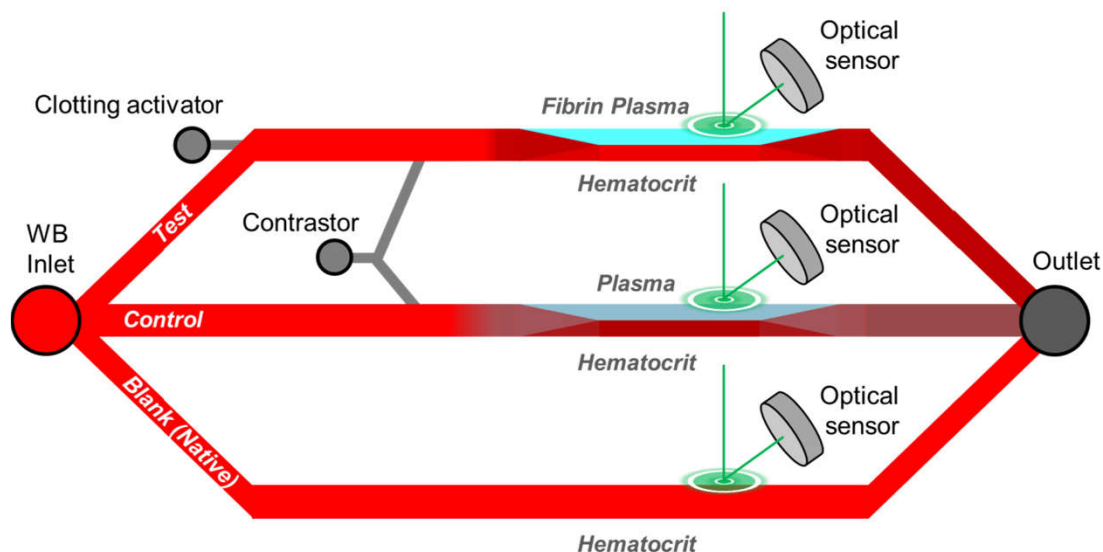
**SUMMARY & KEY NOTES ON SIGNAL
PROCESSING AND MACHINE LEARNING
ASPECTS**



F-POINT ASSAY PROTOTYPE DEVICE



- Aimed to measure FIBRINOGEN
- Especially low FIBRINOGEN
- Works in whole blood (doesn't require sample pre-treatment)
- Rapid: 7 minutes turnaround time
- Pocket-size



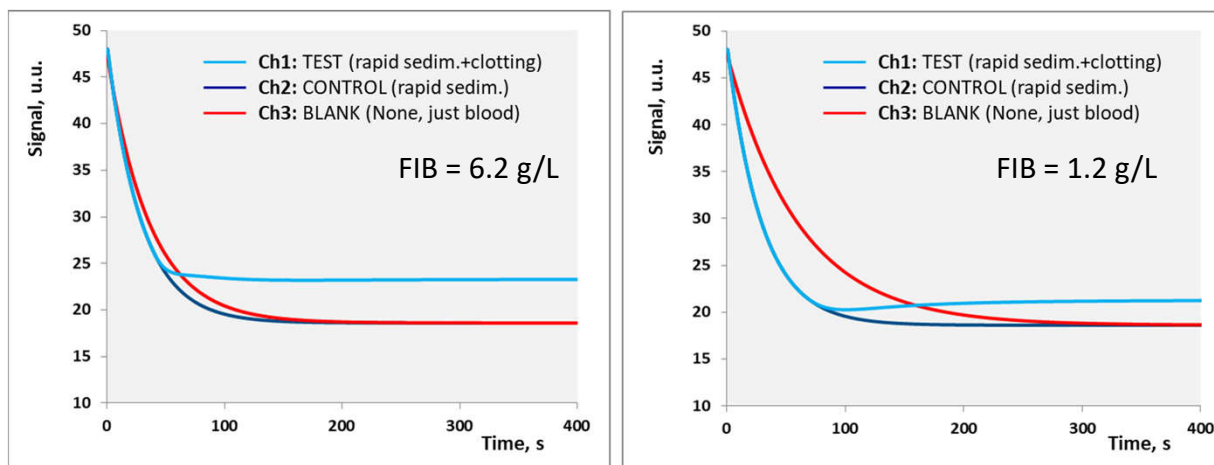


FIG.1. Signals from 3 channels recorded in parallel

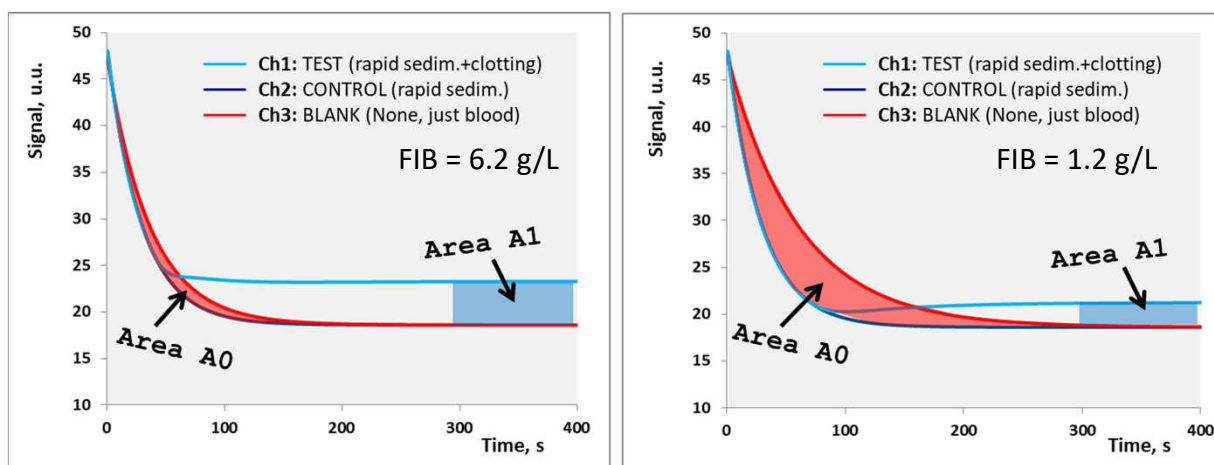


FIG.2. Two Area-Between-Curve values. A1 characterizes fibrin network density; A2 characterizes RBC sedimentation.

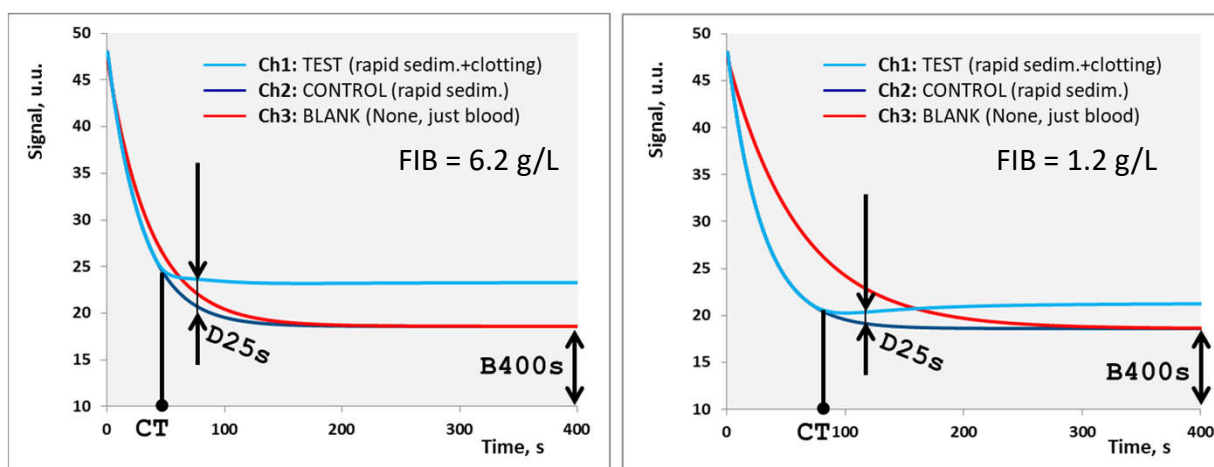


FIG.3. Three timeline values. CT is Clotting Time; B400s is the end value of control channel signal; D25s characterizes fibrin clot growth rate .

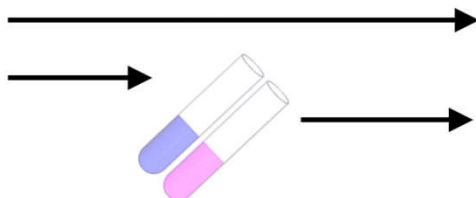
FIB = 1.2 g/L: A0 high / A1 low / CT high / D25s low / B400s is FIB-independent
FIB = 6.2 g/L: A0 low / A1 high / CT low / D25s high / B400s is FIB-independent



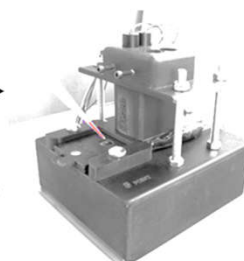
DATA COLLECTION SCHEME



107 normal healthy volunteers donated blood samples, then citrated



Samples randomly divided in 2 equal groups: fibrinogen spiked or partially de-fibrinated



214 samples assayed: 107 normal, 54 spiked, 53 de-fibrinated

DATA

FIB	A0	CT	D25s	A1	B400s
0.4	28	166	0	2	23.9
0.4	30	114	1.2693	1	16.5
0.4	23	88	1.394	11	12.4
0.5	26	100	0	5	16
0.5	23	88	0.6593	5	16

In addition, each sample was HCT assayed by conventional CBC device to have a hematocrit data in hand

DATA SUMMARY

```
> summary(ffD)
      FIB      A0      B400s      D25s
Min.   :0.400  Min.   : 0.00  Min.   :12.40  Min.   : 0.000
1st Qu.:1.825  1st Qu.:10.25  1st Qu.:16.50  1st Qu.: 4.093
Median :3.200  Median :17.00  Median :18.10  Median : 7.393
Mean   :3.256  Mean   :16.59  Mean   :18.55  Mean   : 6.785
3rd Qu.:4.600  3rd Qu.:23.00  3rd Qu.:20.30  3rd Qu.: 9.542
Max.   :6.900  Max.   :33.00  Max.   :27.90  Max.   :13.310

      A1      CT      HCT
Min.   : 1.00  Min.   : 32.00  Min.   :21.00
1st Qu.:13.00  1st Qu.: 42.62  1st Qu.:30.00
Median :15.00  Median : 50.00  Median :33.00
Mean   :16.23  Mean   : 53.11  Mean   :33.74
3rd Qu.:20.00  3rd Qu.: 59.00  3rd Qu.:36.00
Max.   :29.00  Max.   :166.00  Max.   :53.00
```

N = 214
FIB range: 0.4 – 6.9 g/L

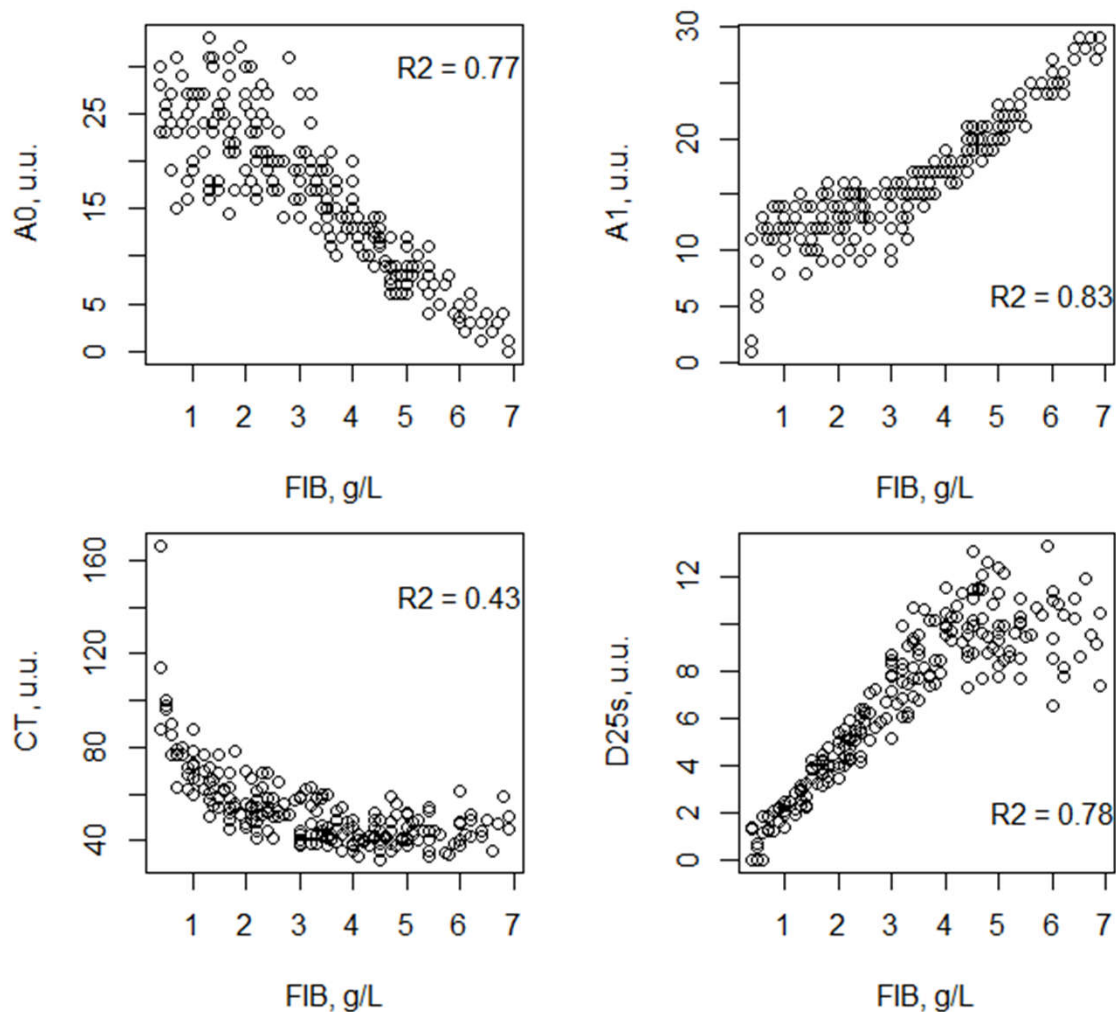


FIG.4. Four extracted parameters as FIB predictors. Looks promising but too weak to be used individually

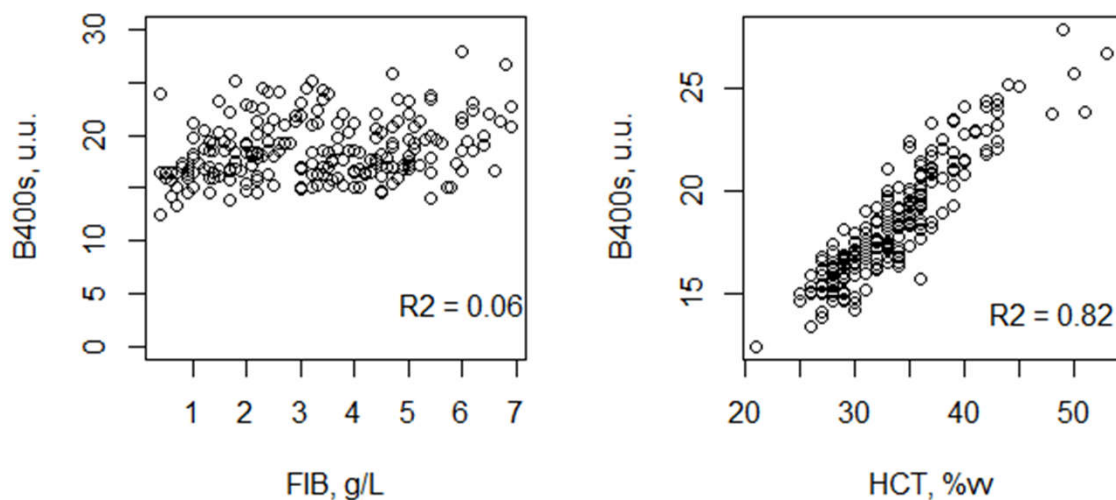


FIG.5. Fifth parameter can be considered as HCT estimator

$$\text{HCT}^{\text{EST}} = \text{B400s} \times 1.82 + 0.03$$



ASSUMPTIONS FOR LOG SCALES, MINMAXS & CUTS

- Log-Log scale significantly improves R2 for kinetic predictors (CT and D25s)
- HCT must be considered as an interaction variable (HCT takes a significant random part of volume) in a form of $\{*(HCT)^{N1,2...}\}$ where $N1, N2$ are unknown

STANDARDIZED INTERPRETABLE PREDICTORS

By-Sedimentation FIB Predictor:

$$ESR.F = cut(A0, >15)/15$$

By-Fibrin FIB Predictor:

$$CLOT_DENSITY.F = cut(A1, <15)/15$$

By-Clotting Time FIB Predictor:

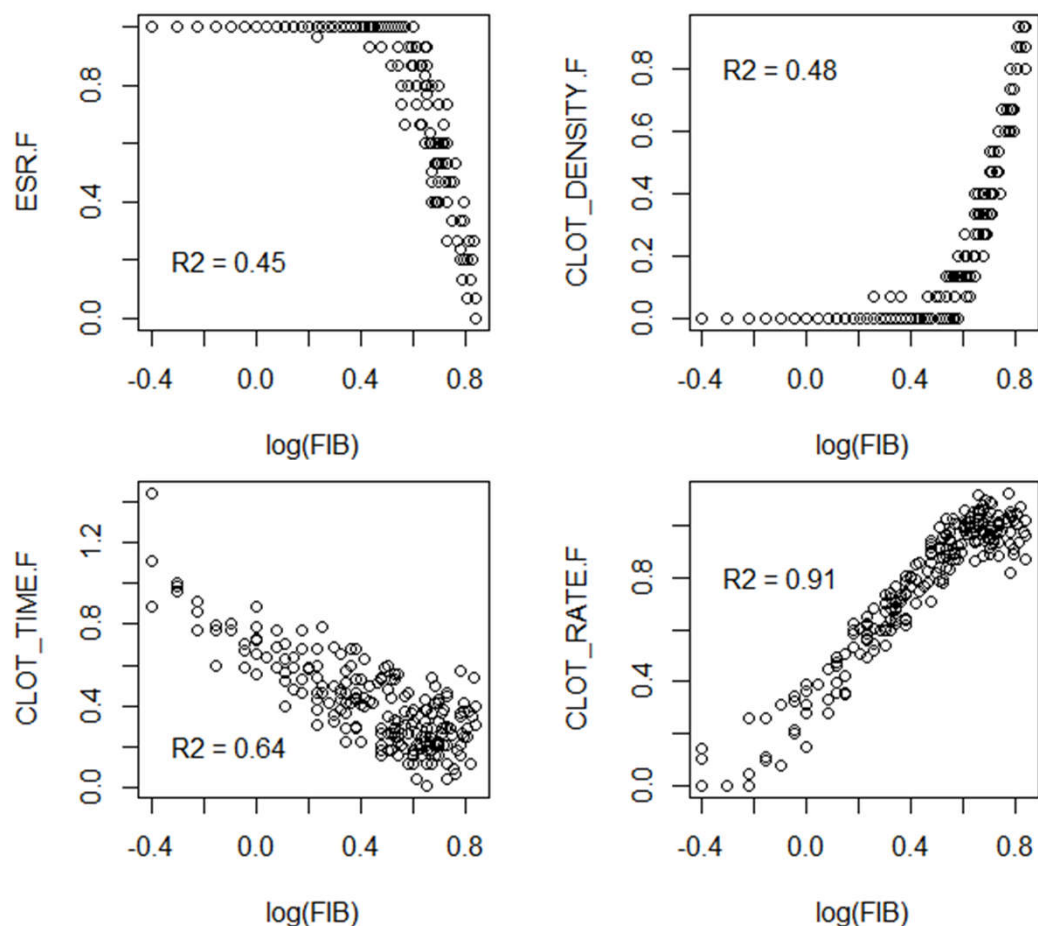
$$CLOT_TIME.F = 2*log(CT)-3$$

By-Coagulation Rate FIB Predictor:

$$CLOT_RATE.F = cut(log(D25s), >1)$$

Interaction with HCT:

$$lLogHCT.F = 2*log10(B400s)-2$$



Cond
Number
= 20.6

FIG.6. Set of standardized interpretable variables as the $\log(FIB)$ predictors



THE MODEL

$$\text{Log}_{10}(\text{FIB}) = -1.1 + 0.7 \cdot \text{PC}^{\text{kinetic}} + 0.2 \cdot \text{PC}^{\text{static}} + 1.1 \cdot \text{LogHCT.F}$$

$$\text{PC}^{\text{kinetic}} = -0.6 \cdot \text{CLOT_TIME.F} + 0.8 \cdot \text{CLOT_RATE.F}$$

$$\text{PC}^{\text{static}} = 0.7 \cdot \text{CLOT_DENSITY.F} - 0.7 \cdot \text{ESR.F}$$

Num. of model vars = 3

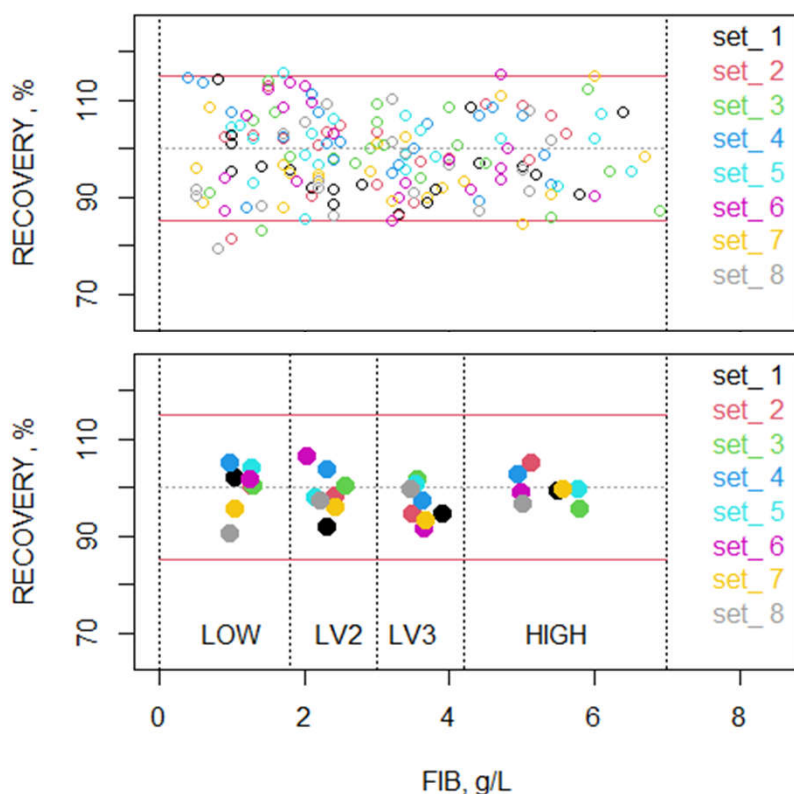
MODEL METRICS BY TRAINING SETS (CROSS-VALIDATION W. EIGHT 91% - RUNS)

Max abs correlation in 3 vars = 0.53

Min R-square = 0.93

Max Cond Number = 4.17

MODEL METRICS BY TESTING SETS (CROSS-VALIDATION W. EIGHT 9%-RUNS)



Bio-analytical accuracy criteria is usually defined by recovery threshold values (+/- 15%).

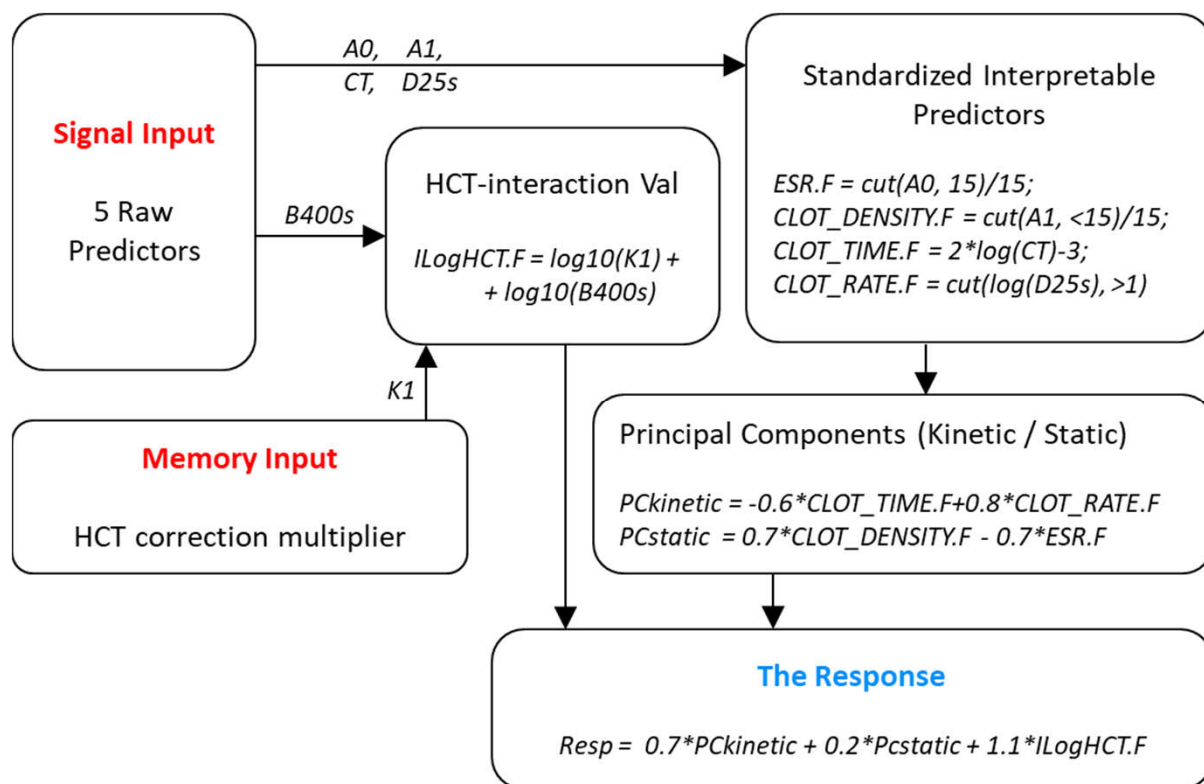
Some separate data can be out of < +/-15% range but **Recovery for each analytical range in average is in**

FIG.7. Recovery plot for all data in 8 testing sets (top) and the mean recovery values for 4 separate analytical FIB ranges.(bottom).



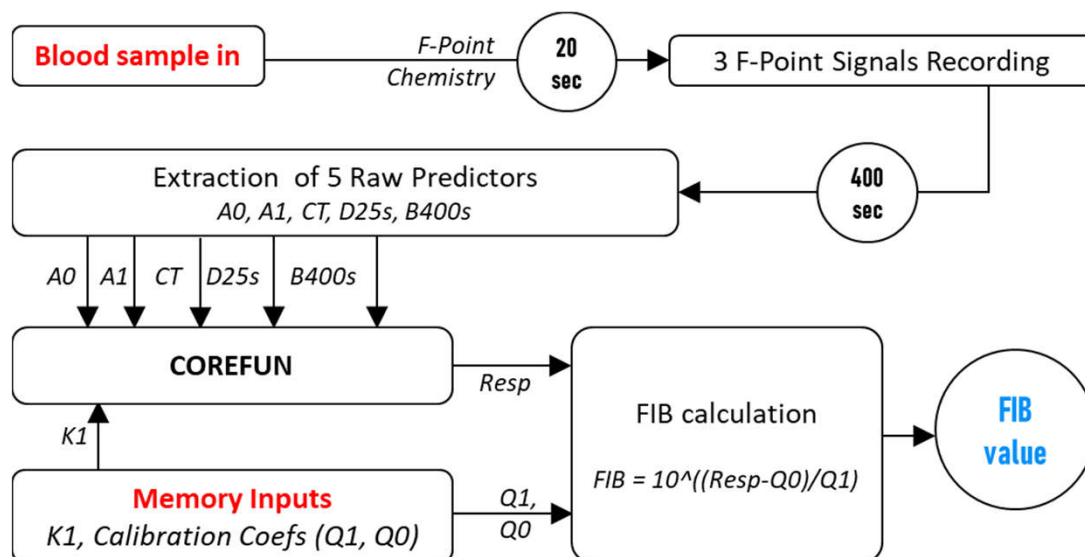
CORE FUNCTION

$Resp = COREFUN(A0, A1, CT, D25s, B400s, K1 = 1)$



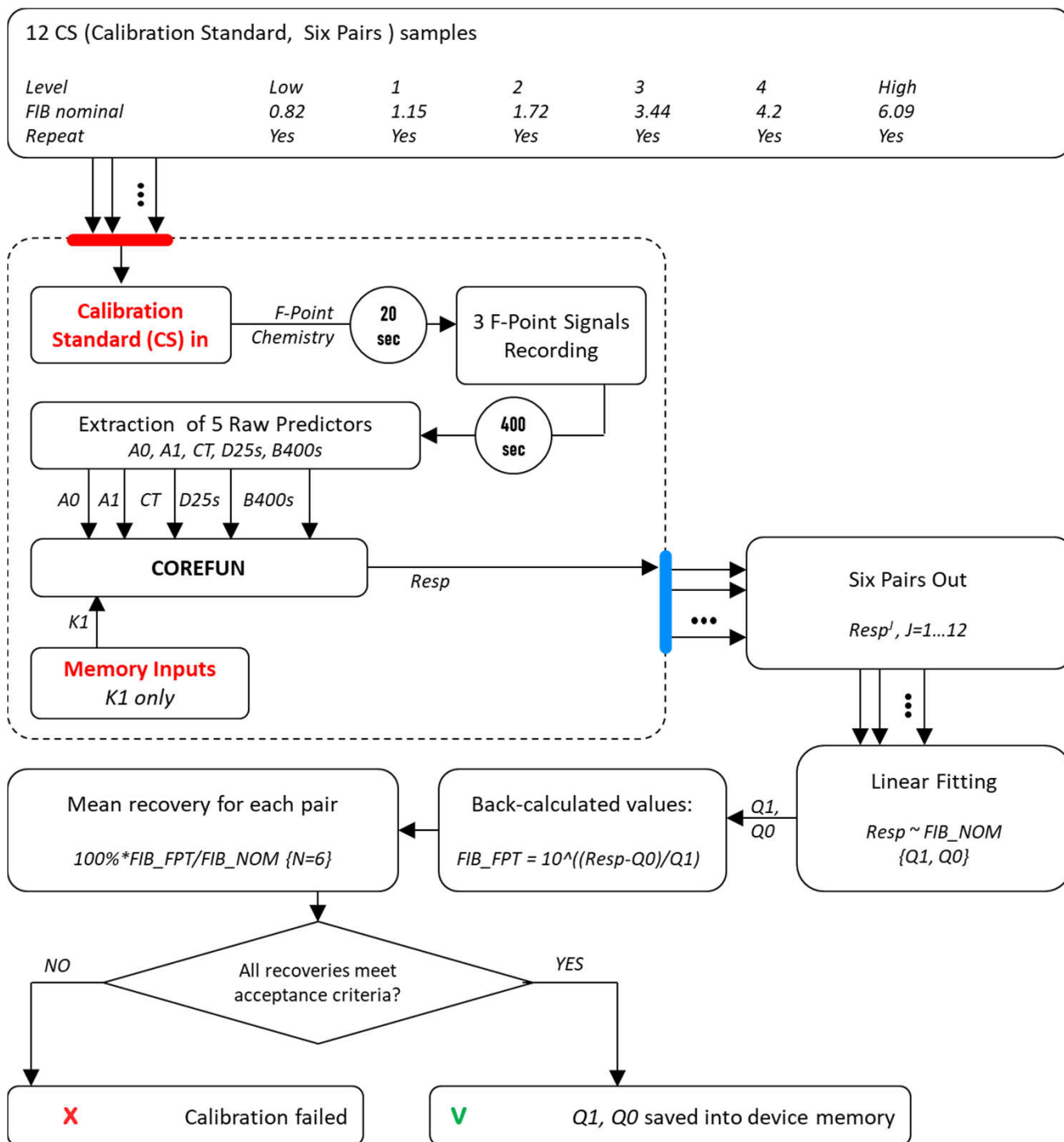
* coefficient K1 is to be defined at periodical HCT-related system adjustment. Default is 1.

MEASUREMENT SCHEME



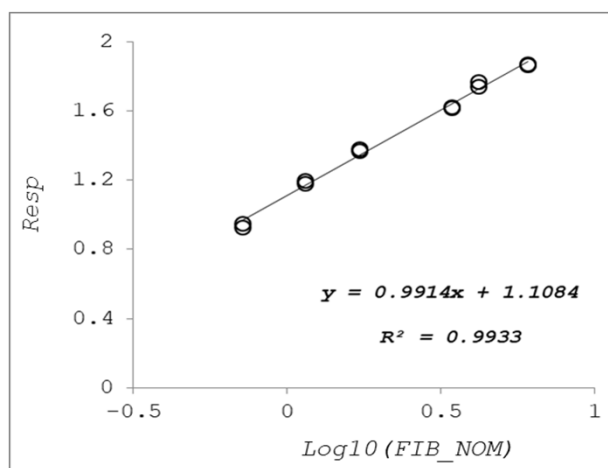


CALIBRATION SCHEME



CALIBRATION STANDARDS, RAW PREDICTORS, RESPONSE & FITTING

CS	K1	FIB_NOM(nominal)	A0	A1	CT	D25s	B400s	Resp(response)
LOW	1	0.72	24	11	86	1.5	16.9	0.94952886
LOW	1	0.72	31	9	80	1.2	17	0.9244608
LEV1	1	1.15	28	12	75	3.3	17	1.19403124
LEV1	1	1.15	25	11	76	3.1	17.1	1.17679593
LEV2	1	1.72	16	14	55	4.4	17.1	1.37994564
LEV2	1	1.72	18	14	54	4	17.2	1.36624521
LEV3	1	3.44	8	18	42	5.5	16.9	1.62030349
LEV3	1	3.44	9	21	43	5.1	17	1.61484069
LEV4	1	4.2	7	23	42	7	17	1.73777372
LEV4	1	4.2	7	24	41	7.2	17.1	1.76555122
HIGH	1	6.09	5	26	37	8	17	1.86315584
HICH	1	6.09	5	26	38	8.3	17.2	1.86796788



Calibration Coefficients

$$Q1 = 0.99$$

$$Q0 = 1.11$$

Back calculated values:

$$\text{FIB_FPT} = 10^{((\text{Resp}-Q0)/Q1)}$$

Fig.8. Calibration plot and a simple linear regression fit

ASSESSMENT OF CALIBRATION QUALITY

CS	FIB_NOM	Mean Resp	FIB_FPT	%Recovery	Acceptance criterion, %	Accepted?
LOW	0.72	0.94	0.67	93.53	80-120	Yes
LEV1	1.15	1.18	1.18	102.33	85-115	Yes
LEV2	1.72	1.37	1.83	106.44	85-115	Yes
LEV3	3.44	1.62	3.27	95.19	85-115	Yes
LEV4	4.2	1.75	4.43	105.49	85-115	Yes
HICH	6.09	1.86	5.72	93.96	85-115	Yes

All criteria of acceptance are met -> Calibration Coefficients are placed into the device memory for further FIB measurements for the real blood samples