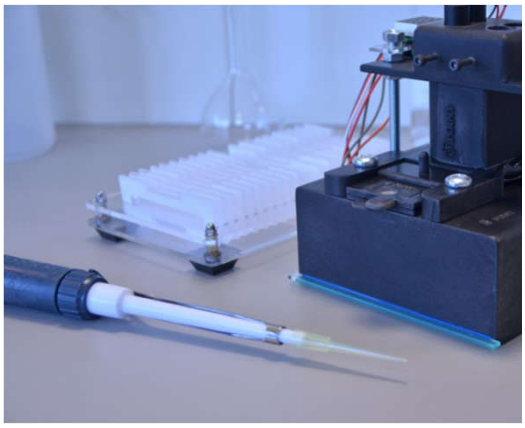
F-POINT ALGORITHM

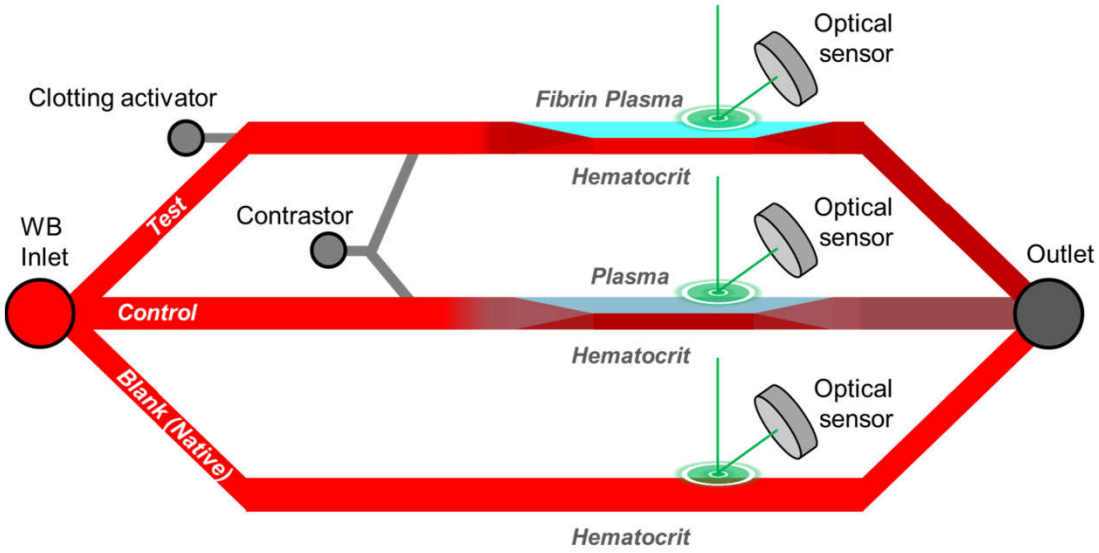
SUMMARY & KEY NOTES ON SIGNAL PROCESSING AND MACHINE LEARNING ASPECTS

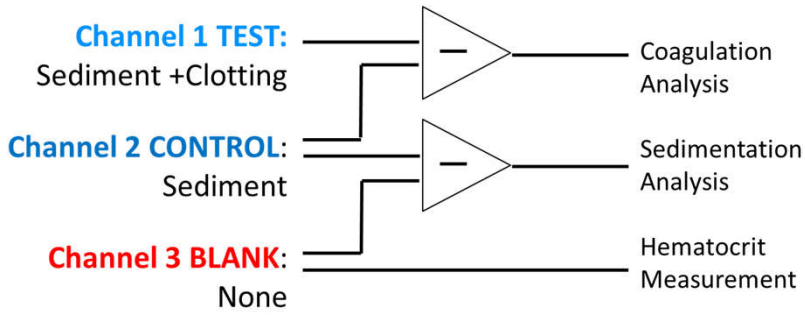
DUBLIN, 16JUL2022

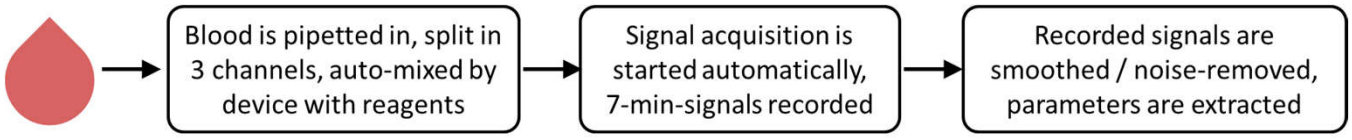
F-POINT ASSAY PROTOTYPE DEVICE



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







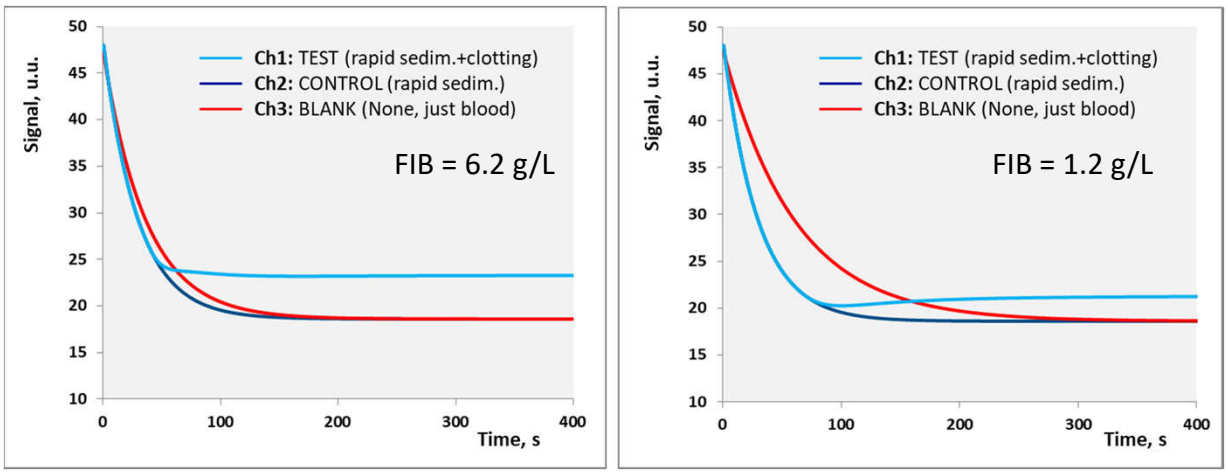


FIG.1. Signals from 3 channels recorded in parallel

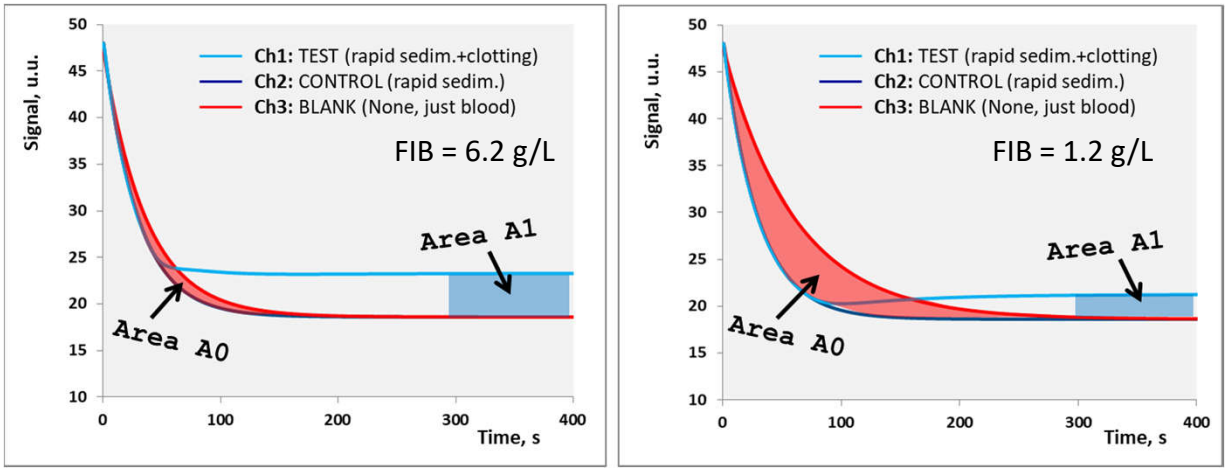


FIG.2. Two Area-Between-Curve values. A1 characterizes fibrin network density; A2 characterizes RBC sedimentation.

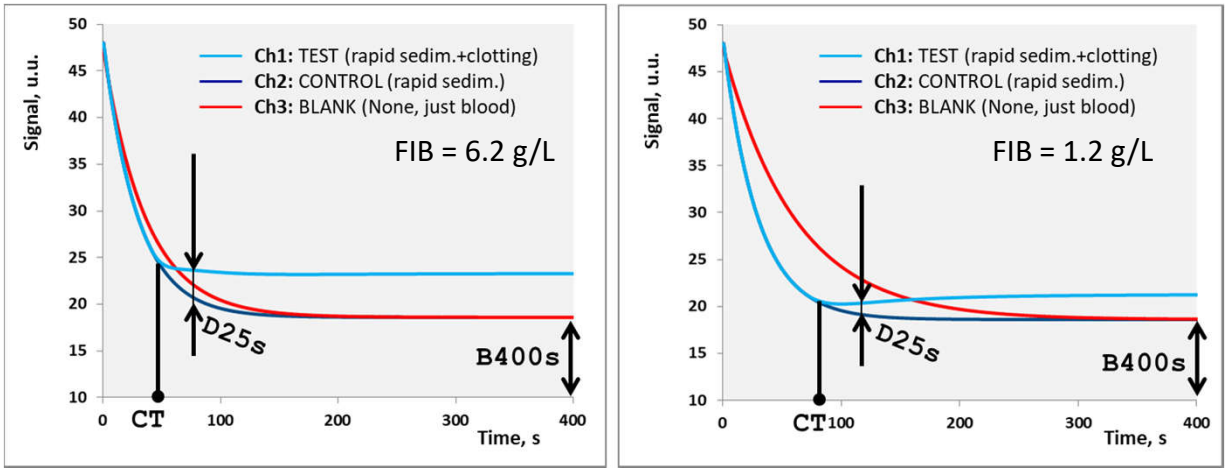
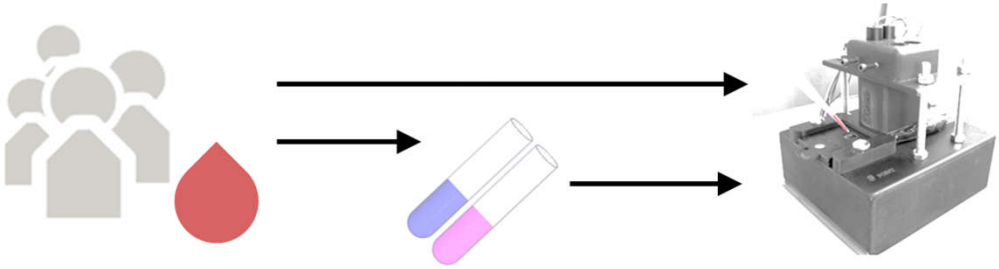


FIG.3. Three timeline values. CT is Clotting Time; B400s is the end value of control channel signal; D25s characterizes fibrin clot growth rate .

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	98	0.6582		

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

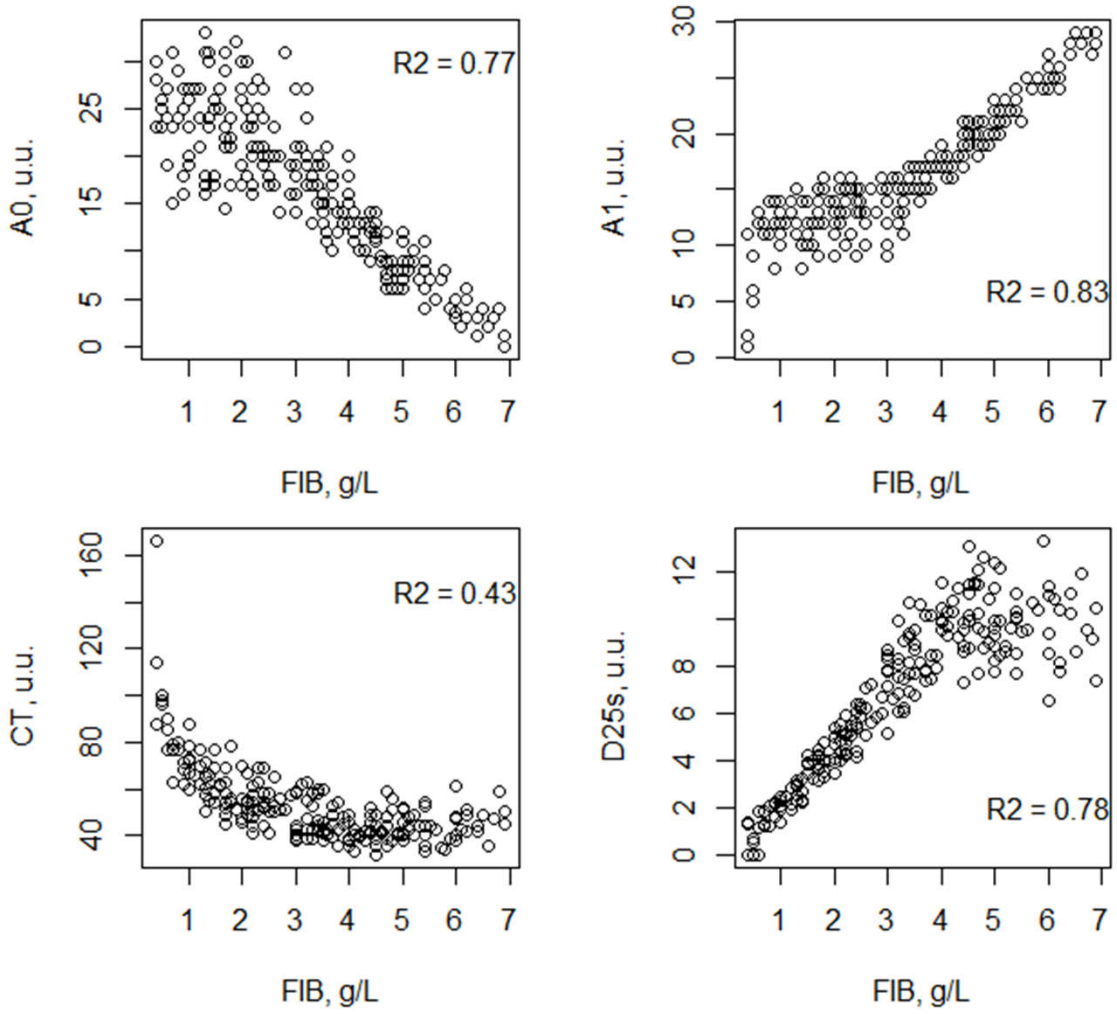


FIG.4. Four extracted parameters as FIB predictors. Looks promising but too weak to be used individually

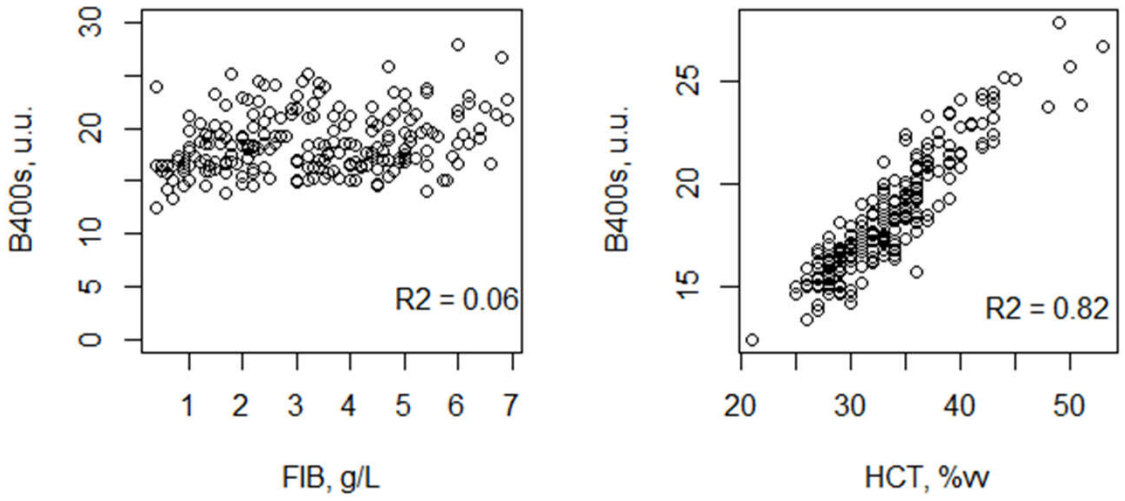


FIG.5. Fifth parameter can be considered as HCT estimator

HCT^{EST} = B400s*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

STANDARTIZED 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:	*ILogHCT.F = 2*log10(B400s)-2*

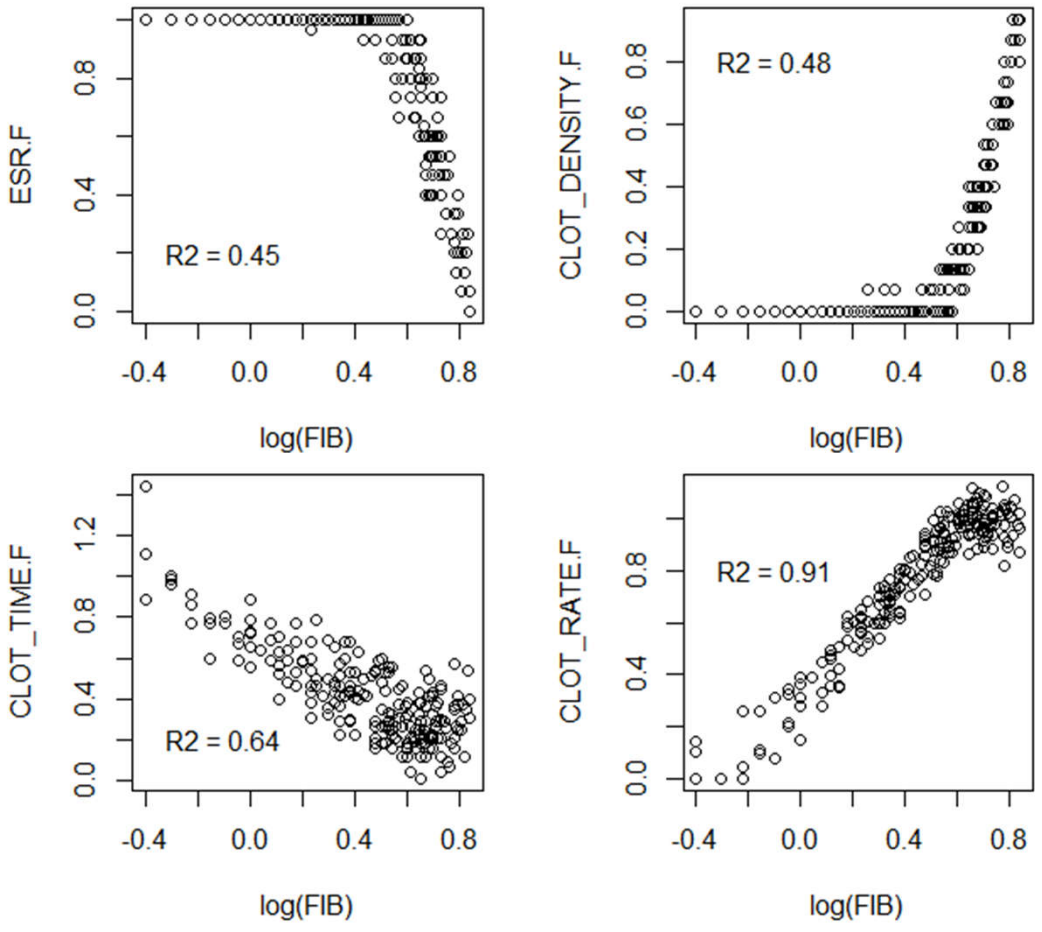


FIG.6. Set of standardized interpretable variables as the log(FIB) predictors

THE MODEL

$$Log10(FIB) = -1.1 + 0.7*PC^{kinetic} + 0.2*PC^{static} + 1.1*ILogHCT.F$$

$$PC^{kinetic} = -0.6*CLOT\_TIME.F + 0.8*CLOT\_RATE.F$$
$$PC^{static} = 0.7*CLOT\_DENSITY.F - 0.7*ESR.F$$

Num. of model vars = 3

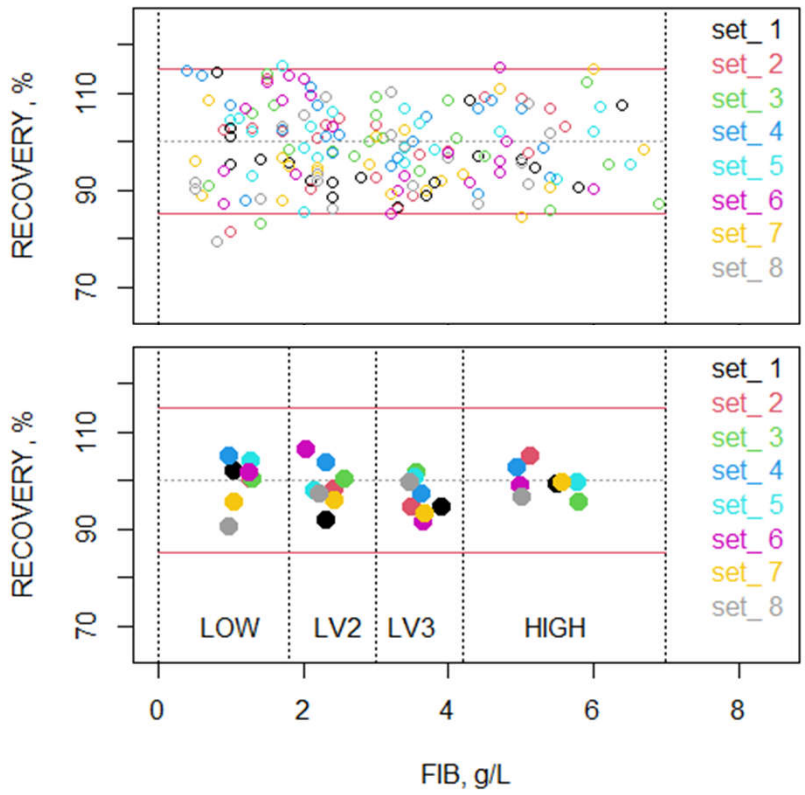
MODEL METRICS BY TRAINING SETS (CROSS-VALIDATION W. EIGHT 91% - RUNS)

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)



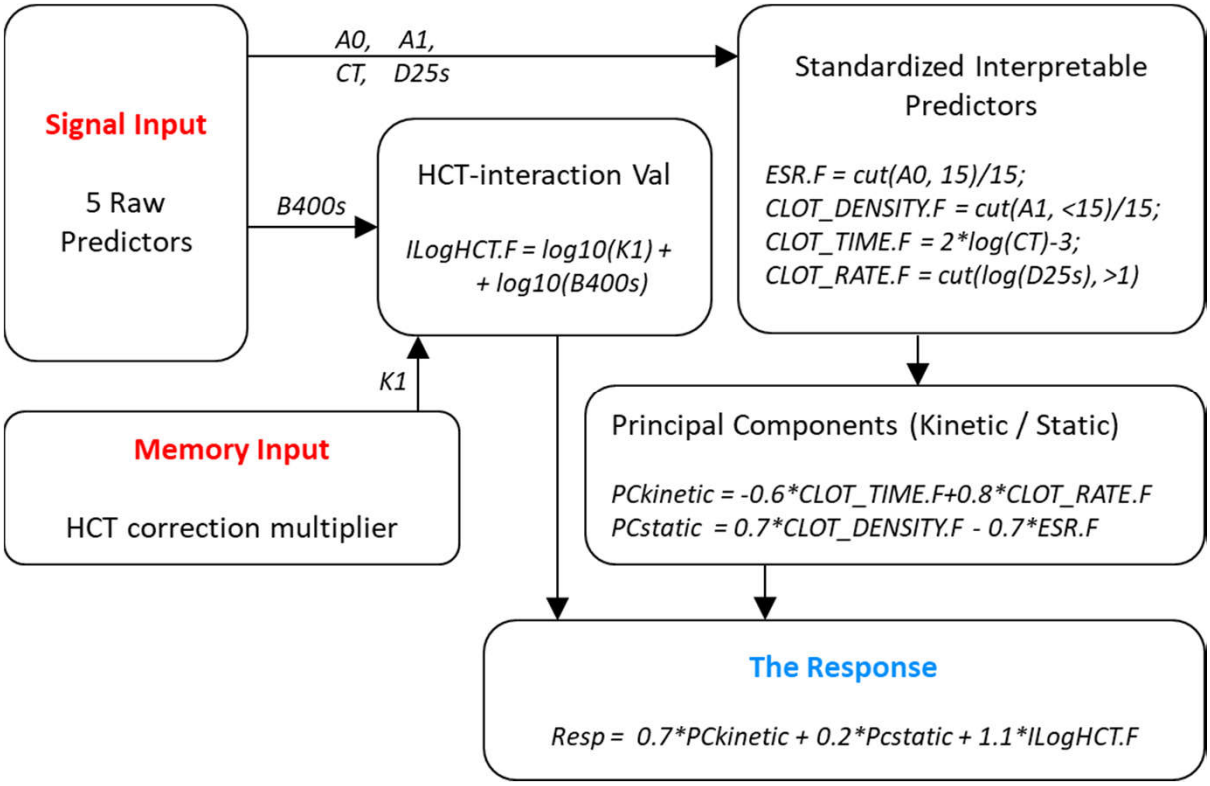
Bio-analytical accuracy criteria is usually defined by recovery threshold values (+/- 15%).

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).

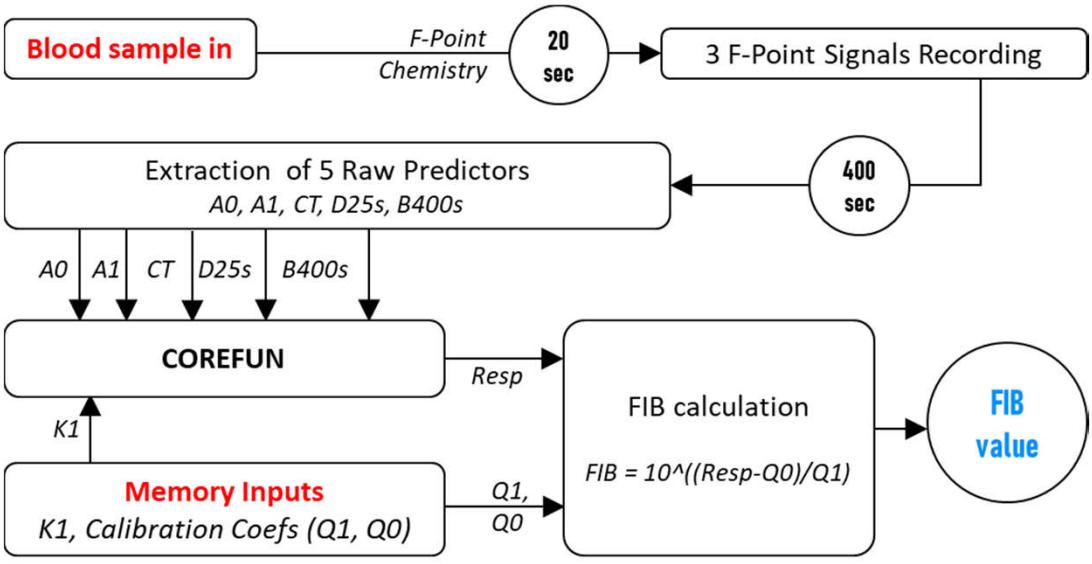
CORE FUNCTION

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

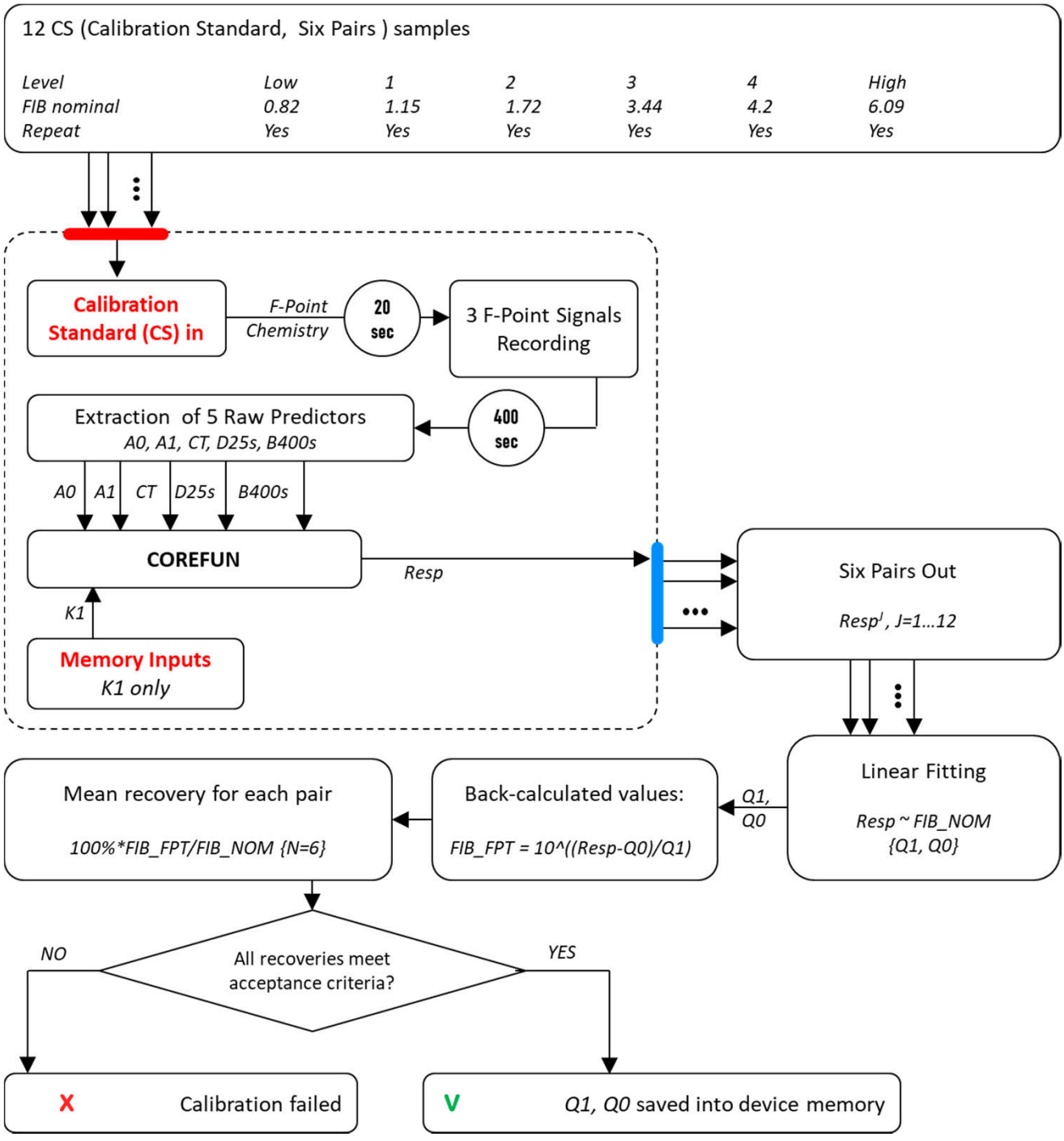


* coefficient K1 is to be defined at periodical HCT-related system adjustment. Default is 1.

MEASUREMENT SCHEME

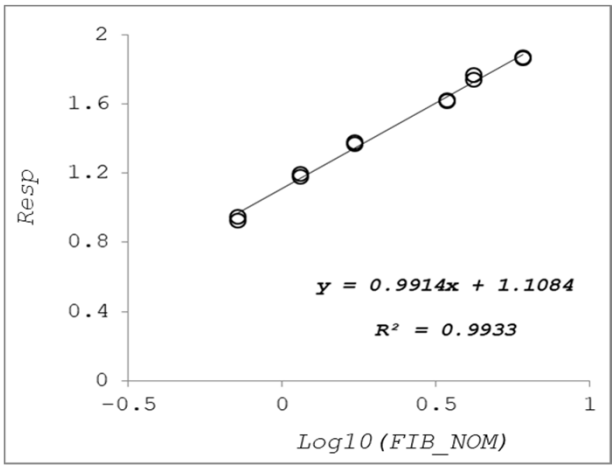


CALIBRATION SCHEME



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:

FIB_FPT = 10^((Resp-Q0)/Q1)

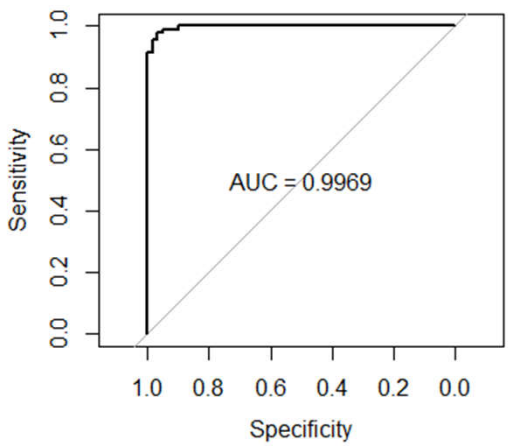
Fig.8. Calibration plot and a simple linear regression fit

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

HYPOFIBRINOGENAEMIA (FIB < 1.8 g/L)



F-Point as a descent classifier

REAL MEASUREMENT: A WHOLE BLOOD SAMPLE OF UKNOWN FIB AND HCT

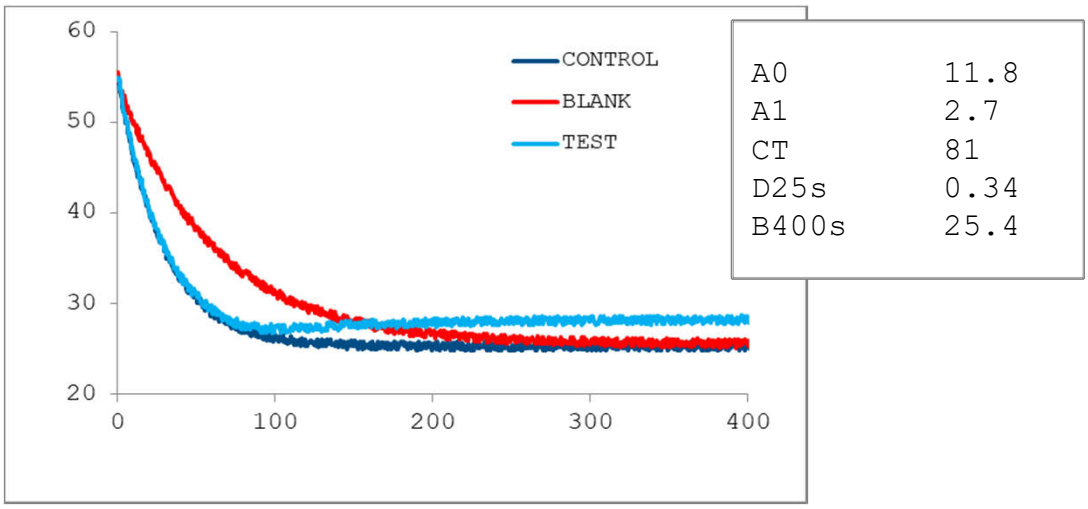


Fig.9. Real 3 channel signals recorded by F-Point and extracted set of raw predictors

Resp = 1.03; Q1 = 0.99, Q0 = 1.11 (taken from the last calibration)

FIB = 10^((Resp-Q0)/Q1) = 0.83 g/L

ESTIMATION OF HCT AS A BONUS

$HCT^{EST} = 1.82*K1*B400s = 46.2$ *%v.v.*

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