

Stability Analysis of Kalman Filter Based Delivery Rate Computation Algorithm for IV Administered Anesthetic Propofol

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Introduction

The controlled delivery of intravenous (IV) anesthetic, such as propofol, aims at fast and safe achievement and maintenance of a depth of hypnosis, by ensuring appropriate effect site (i.e. brain) exposure to the drug. Today, such drugs are regularly injected by Target Controlled Infusion (TCI) systems, piloted by an open-loop algorithm based on Pharmacokinetic (PK) models. However, clinical conditions may markedly alter propofol pharmacokinetics and actual concentrations could significantly differ from predicted ones, leading to important under- or over-exposure. The situation could be improved by closing the loop with sensors providing regular real measurements of the anesthetic concentration in body fluids. We present a closed-loop algorithm based on the classic open-loop algorithm presented by Shafer et al [1] combined with a Kalman filter using real-time plasma measurements. We perform stability analysis of this algorithm by accounting for realistic measurement noise, periods and delays.

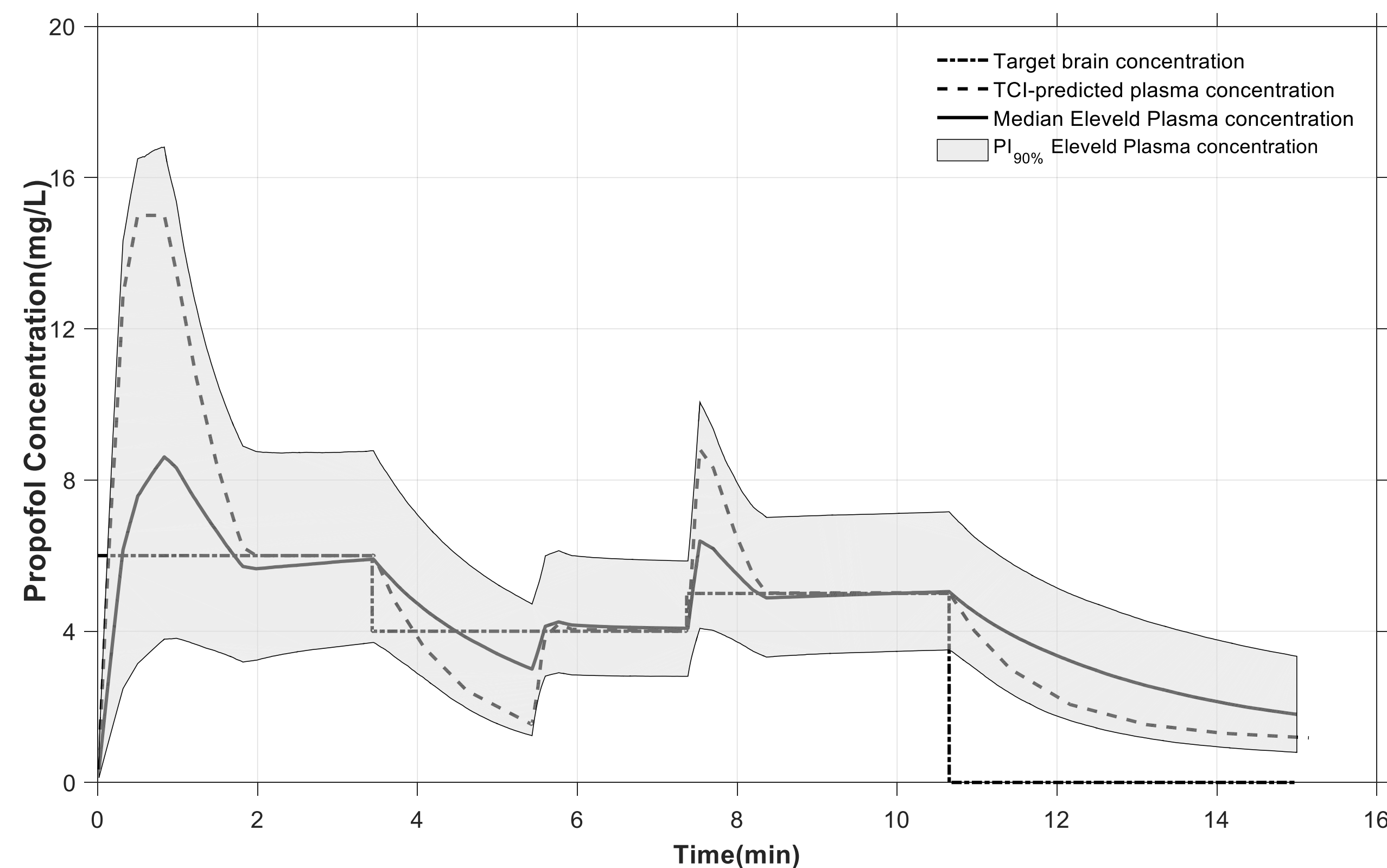
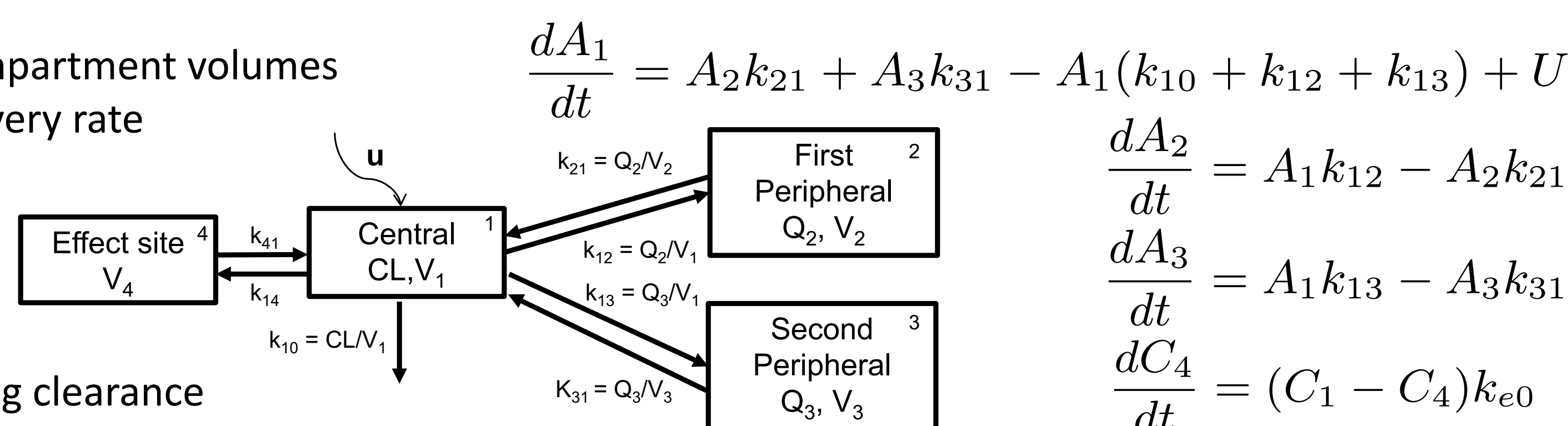


Fig1. Comparison of Schnider[2] and Eleveld [3] models : median Concentration-Time (CT) profile with 90% prediction interval (PI90%) of 10000 virtual subjects with identical demographic characteristics (36 years old, female, body weight 70 kg, and height 170 cm)[4]

Pharmacokinetic Modeling

V_i - compartment volumes

U - delivery rate



CL - drug clearance

Q_i - inter-compartmental clearances

$C_i = A_i/V_i$ - is the drug concentration in i^{th} compartment

Inter-patient variability: $PAR_k^j = PAR_k * e(\eta_k^j)$

were PAR_k^j is the k^{th} PK parameter of j^{th} individual; PAR_k is the average population value, and η_k^j is a random variable with $N(0, \omega_k^2)$

Intra-patient variability: $Y_n^j = C_n^j + \sqrt{prop * (C_n^j)^2 + add * EPS_n^j}$

were Y_n^j - measured concentration at time n , C_n^j - predicted concentration; $prop$ and add are the squared components of mixed Eleveld error model [3]; and EPS_n^j is the n_j^{th} random effect with $N(0,1)$

Controlling Closed-loop Algorithm

Feedforward Shafer's [1] algorithm

Algorithm 1: A_4 with a unit rate during 10 seconds

```
Data:  $a(0) = [0, 0, 0, 0]$ ,  $j = 1$ ;
Result:  $t_{peak}, E[]$ 
1 while  $E[j] > E[j-1]$  do
2   if  $j < 11$  then
3      $u[j] = 1$ ;
4   else
5      $u[j] = 0$ ;
6   end
7    $a[j] = a[j-1] + Fa[j-1] + Bu[j]$ ;
8    $E[j] = a_4$ ;
9 end
10  $t_{peak} = j - 1$ ;
```

Algorithm 2: $A_4[n : n + t_{peak}]$ with no drug injected

```
Data:  $g_1[0] = A_1$ ,  $g_2[0] = A_2$ ,  $g_3[0] = A_3$ ,  $g_4[0] = A_4$ ,  $u[] = 0$ ;
Result:  $G_4[1 : t_{peak}]$ 
1 for  $j = 1$  to  $t_{peak}$  do
2    $g[j] = g[j-1] + Fg[j-1]$ ;
3    $G_4[j] = g_4$ ;
4 end
```

$A_4 = G_4[j] + E[j]$, were peak value of A_4 is reached at j_{peak}

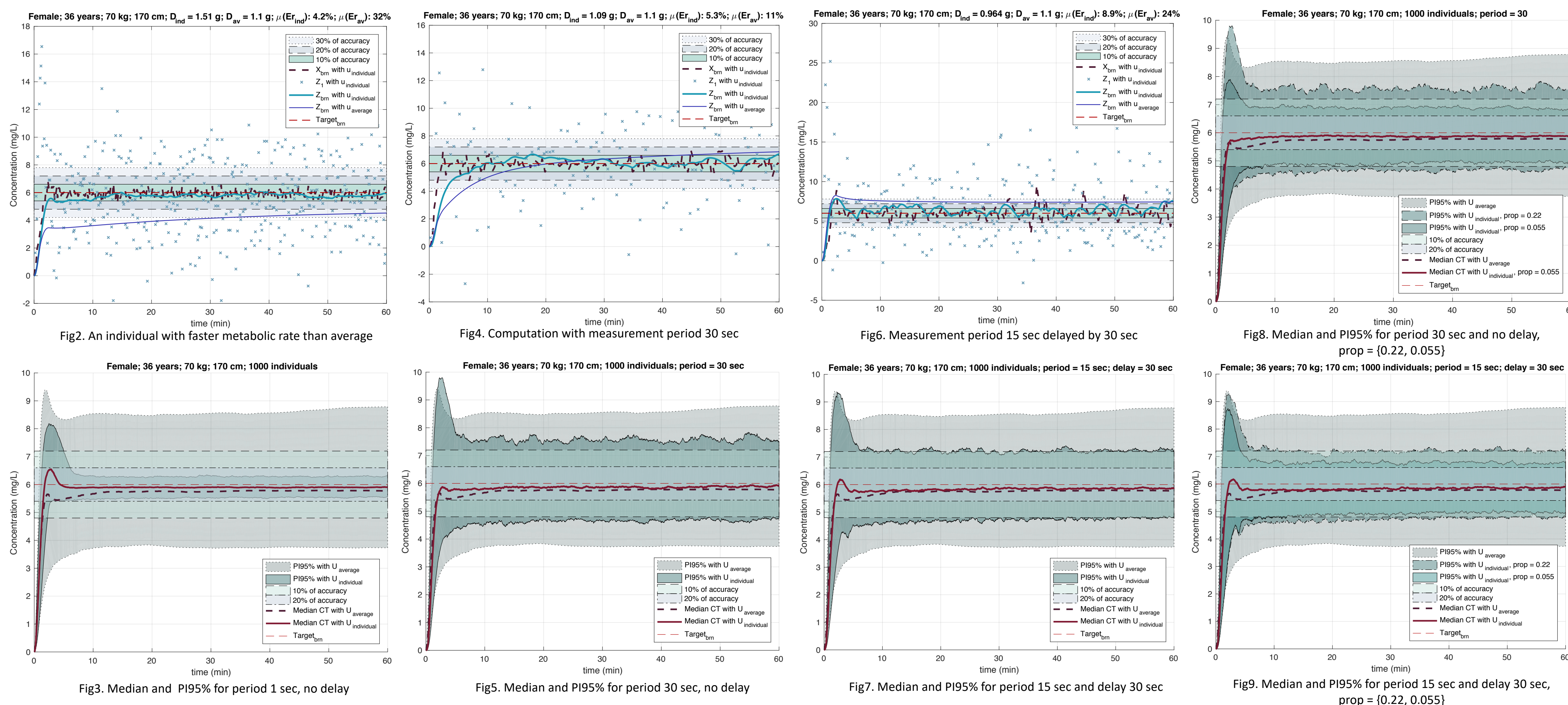
$u = \frac{targetA_4 - G_4[j_{peak}]}{E[t_{peak}]}$ - equation is solved for u and j_{peak} simultaneously

Kalman filter

Algorithm 3: Classical Kalman filter implementation

```
1 Predict:
2  $\hat{X}_{n|n-1} = F\hat{X}_{n-1|n-1} + Bu_{n-1}$  // a priori state est.
3  $P_{n|n-1} = FP_{n-1|n-1}F^T + Q$  // a priori covariance est.
4 Update:
5  $\tilde{d} = y_n - H\hat{X}_{n|n-1}$ 
6  $S_n = HP_{n|n-1}H^T + R_n$ 
7  $K_n = P_{n|n-1}H^T S_n^{-1}$ 
8  $\hat{X}_{n|n} = \hat{X}_{n|n-1} + K_n\tilde{d}$  // a posteriori state est.
9  $P_{n|n} = (I - K_nH)P_{n|n-1}$  // a posteriori covariance est.
```

Analysis Results



Conclusion

- The results show the algorithm stability with different measurement periods and delays with the very high Eleveld model predicted variability of plasma measurements.
- In reality, this variability is expected to be much lower contributing to better stability of the algorithm.
- Still our work shows that the use of the presented algorithm ensure both more precise and safer plasma and effect size exposures than currently achieved with open-loop TCI pumps.

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