EVALUATION OF ADAPTIVE AND NON-LINEAR PKPD MODELS FOR BIVALIRUDIN IN POST-CARDIAC SURGICAL PATIENTS

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Introduction: Bivalirudin is a direct thrombin inhibitor that is known to decrease thrombo-embolic complications due to heparin-induced thrombocytopenia (HIT). It is an anticoagulant that raises the partial thromboplastin time (PTT). Although it is FDA-approved for catheter interventions only, it is increasingly being used for prolonged anticoagulation in patients after cardiac surgery. Yet, experience with dosing in this setting is sparse. A mathematical model of the dose-response relationship may be useful to guide dosing of bivalirudin in the future.

Hypotheses:

- The patient's PTT response can be simulated with a one-compartment PKPD model.
- Performance of the model can be improved when taking the fluctuating, renal elimination into account.
- Modeling tachyphylaxis and allowing for an adaptive adjustment based on past performance will improve the model.

Methods: In a retrospective chart review of 149 post-cardiac surgical ICU patients, the PTT, the estimated GFR and the continuous infusion rate of bivalirudin was collected. After randomly assigning subjects to a derivation and a validation cohort, eight PKPD models (linear, non-linear, each with or without tachyphylaxis and adaptive capability) were fitted to the derivation data resulting in coefficients which were averaged. The non-linear PKPD models incorporate variable eGFR while the linear models do not. The derived "average" models were then tested in the validation cohort.

Results: In the derivation and validation cohorts of 74 and 75 patients, respectively, the median duration of bivalirudin infusion was similar at 12.3 and 8.8 days. Figure 1 illustrates the non-linear model with and without the adaptive capability. When testing the derived models in each patient of the validation cohort we found root-mean-square (RMS) errors (between the actual and predicted PTT) and Pearson's correlation coefficients. The mean values for the 75 validation patients are given in table 1.

Conclusions: We found that the patient's PTT response to bivalirudin can be simulated with PKPD models leading to mean RMS errors ranging from 13.8 to 23.1 seconds. The predicted and actual PTT courses show moderate correlation. The predictive power of the model is greatly improved when an adaptive feature is included. This allows the model to "learn" from past discrepancies between actual and predicted PTTs. Modeling of tachyphylaxis during prolonged infusions did not improve model performance (see table 1). The addition of a non-linear component accounting for changing eGFR did not significantly improve accuracy.

Table 1. Comparing actual to predicted PTT
Root-Mean-Squared error / Pearson's correlation coefficient

	Linear model	***Non-linear model***
Basic model	23.1/ 0.53	22.8/ 0.53
With tachyphylaxis	22.8/ 0.53	21.7/ 0.52
With adaptation	13.8/ 0.55	13.9/ 0.55
With both tachyphylaxis and adaptation	13.8/ 0.54	14.0/ 0.55

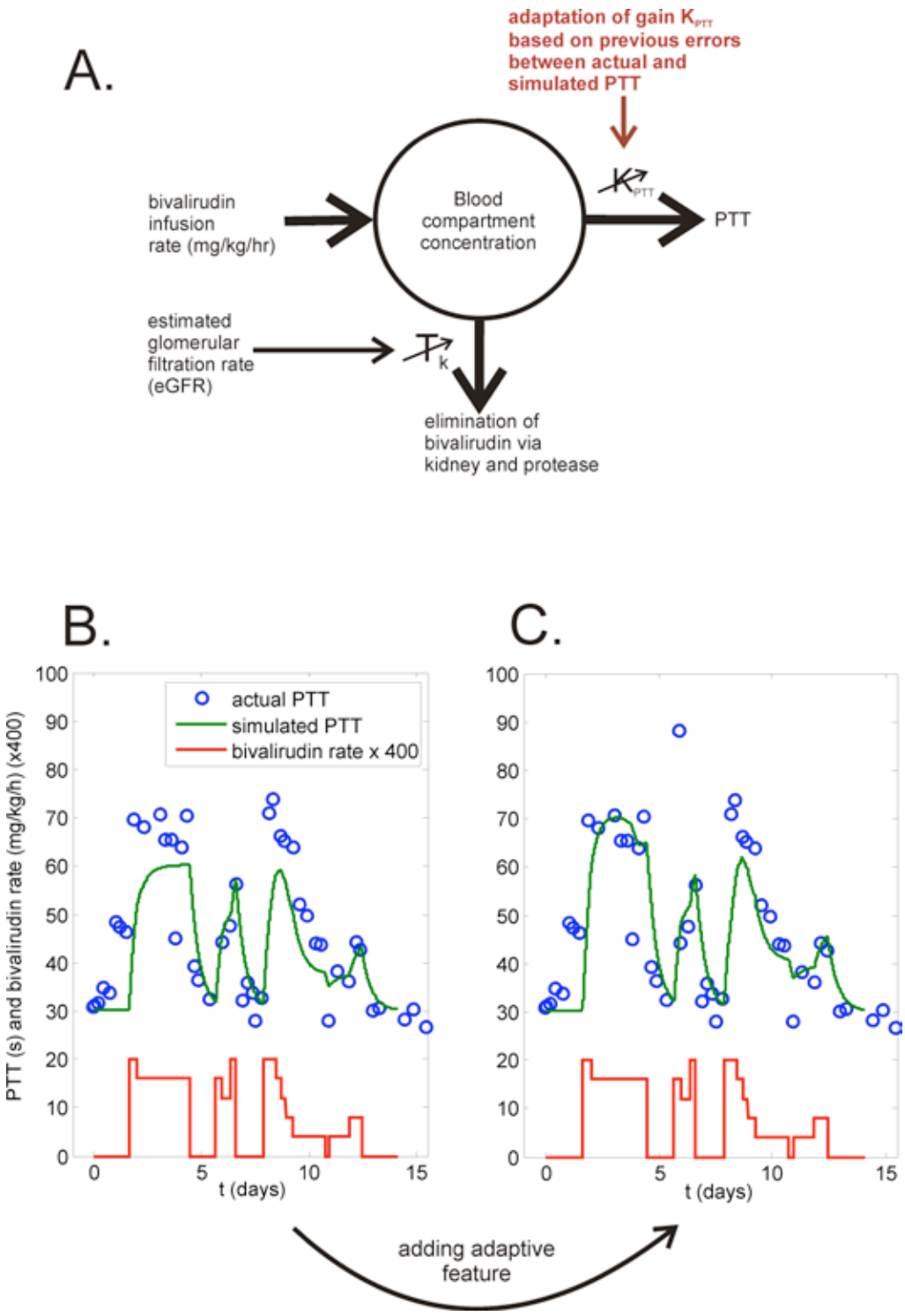

Figure 1. Nonlinear PKPD model (panel A) with an adaptive gain KPTT. As shown in a sample patient (panels B and C), the addition of the adaptive feature improves the fit. The root-mean square (RMS) error decreases from 9.6 to 8.5 (s) in this patient.