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Multicompartment Urea Kinetics in Well-Dialyzed Children

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Multicompartment Urea Kinetics in Well-Dialyzed Children

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Running Title: Pediatric urea kinetics

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Multicompartment Urea Kinetics in Well-Dialyzed Children:

Abstract:

Background: We have reported catch-up growth with hemodialysis (HD) of ~15 h/wk (*J Pediatr '99;134:464*) [1]. Without an equilibrated post-treatment BUN, the variable volume single pool (VVSP) model will not account for urea rebound, inflating estimated HD dose (K_dt/V). A 2 pool model (FVDP) predicts rebound, but requires fixed compartment volumes for the equations to be solvable in closed form, also inflating K_dt/V.

Methods: We develop an approximate perturbation solution (WKB method) to a variable volume, 2 pool (VVDP) model. Estimated model parameters are compared to the results of equilibrated kinetic studies with measured clearance K_d (n=17). Once the model is validated, we reanalyse 292 kinetic studies from our earlier cohort, considered well-dialyzed on the basis of growth rates (n=12, mean annual change in height standard deviation score +0.31, mean follow-up 26 mo).

Results: For the VVSP, FVDP, and VVDP models, respectively, the mean errors were: K_dt/V: 0.22±0.07, 0.29±0.17, 0.06±0.07 (ANOVA p<0.001); urea distribution volume V/Wt(%): -8.2±4.2,–9.1±3.0,–2.2±3.6 (p<0.001); Sequential studies confirmed reproducibility, with coefficient of variation ≤5%. In the earlier cohort, comparison of the VVSP and VVDP models yielded: K_dt/V: 1.91±0.35 vs 1.76±0.33 (*p*<0.001); normalised protein catabolic rate (nPCR g/kg/d) 1.56±0.39 vs 1.52±0.38 (*p*<0.001); K_d (whole blood, ml/kg/min) 4.8±0.9 vs 4.4±0.8 (*p*<0.001).

Conclusion: This VVDP model yields reliable estimates of K_dt/V and other kinetic parameters using standard BUN sampling. Analysis of patients previously characterised as well-dialyzed on the basis of growth rates clarifies the HD dose needed to sustain normal growth.

Keywords: hemodialysis, growth, pediatrics

Running Title: Pediatric urea kinetics

Introduction:

Based largely on adult studies correlating hemodialysis (HD) mortality and morbidity with small solute clearance (urea $K_d t/V$), the 1997 Dialysis Outcome Quality Initiative (DOQI) recommended monthly urea kinetic studies in children receiving maintenance HD, suggesting a minimum delivered $K_d t/V$ of 1.2 [2]. Extrapolation from adult studies may be problematic, as more appropriate pediatric outcome measures - such as growth, school performance, or pubertal development - might lead to very different conclusions as to the relative importance of the small molecular weight toxins for which urea is a surrogate marker. Prior to the introduction of recombinant human growth hormone (rhGH), mean annual loss in height standard-deviation score (ΔHSDS) in prepubertal HD patients was -0.4 to -0.8 SD/year [3]. However, we have recently described normal growth rates, catch-up growth, and normal puberty with intensive nutritional support and hemodialysis clearance in prepubertal patients treated without rhGH [1]. With a weekly treatment time of ~ 15h and a single pool urea $K_d t/V$ of ~ 2.0, the mean annual ΔHSDS was > +0.3 SD/year, and predicted final adult height fell generally within 2 SD of genetic potential.

The standard variable volume, single pool (VVSP) urea kinetic model recommended for this purpose is also less satisfactory in children, predicting higher than observed blood urea nitrogen (BUN) concentrations during dialysis and failing to account for post-dialysis urea rebound, felt to reflect treatment-induced compartment effects [4, 5, 6, 7]. The net result is that dialysis appears spuriously more effective, with overestimation of dialyzer clearance K_d, reduction in apparent urea distribution volume V, and attendant inflation of urea $K_d t/V$. Although fully equilibrated (1h) post-treatment BUN samples will avoid these pitfalls, this was not felt to be practical on a routine basis [2].

A multicompartmental model with intracellular (ICF) and extracellular (ECF) fluid spaces in series does predict intercompartmental disequilibration and urea rebound, but fixed compartment volumes are typically assumed to permit closed-form solutions (i.e. formulae predicting BUN as a function of

time and other parameters) [8, 9]. If used to estimate unknown model parameters, this approach leads to more egregious errors than the single pool model, particularly in smaller patients with significant interdialytic weight gain. Although the differential equations are readily formulated for more realistic models, and even integrated numerically for investigational purposes, closed-form solutions are usually not possible, hindering routine application in a clinical setting. In the physical sciences, perturbation methods are often used to formulate approximate closed-form solutions to otherwise intractable differential equations [10]. These solutions rely on identification of 'small' parameters in the governing equations and are typically expressed as the solution to the simpler, solvable system in which these quantities are neglected (the *unperturbed* model) *plus* a correction term (*perturbation*).

Here, we reformulate a two compartment, variable volume model (VVDP). A straightforward perturbation expansion yields the VVSP model as unperturbed solution plus a correction term incorporating the effects of finite intercompartmental urea permeability. This solution fits well with the experimental data and furnishes reliable estimates of equilibrated kinetic parameters in typical pediatric HD studies. We then retrospectively reanalyse 292 monthly urea kinetic studies collected on the prepubertal patients from our earlier report of growth, felt to be unequivocally well-dialyzed on the basis of growth rates and pubertal development. These data furnish an estimate for the dialysis dose needed to sustain normal growth and development.

Patients and methods:

The 12 patients described in our earlier report, all the prepubertal patients receiving long-term maintenance HD in our center from 1991 until the introduction of rhGH in 1997, are fully characterised in [1], including details of diagnosis, treatment, nutritional supplements, metabolic control, routine urea kinetic studies, and growth. Validation of the VVDP model involved 15 patients presented in Table 1: From our unit, 11 equilibrated urea kinetic studies were performed (mean treatment duration 283 ± 27 min), with patients 1 and 2 furnishing duplicate studies separated from the initial assessment by 3 and

6 months, respectively. Published data were reanalysed for six historical cases, included because of a relatively short treatment duration (142 ± 30 min) [5, 6]. Dialyzer urea clearance K_d (whole blood, ml/min) was measured by the AV gradient method (appendix, eq. 1). The blood pump was calibrated prior to each study, and a commercial indicator-dilution technique was used to measure blood flow and exclude access recirculation (Transonic^{TM}) [11], the latter corroborated in each case by the multiple-BUN method (eq. 2). BUN sampling (mM, whole blood) was typically hourly from the inlet side of the dialyzer during treatment ('slow-flow ' technique [2]) and included pre-dialysis(C_0), end-dialysis (C_1), equilibrated one hour post-dialysis (C_{1eq}), and a second pre-dialysis sample (C_2) before the next treatment. The end-dialysis specimen was drawn 5 minutes after dialysate flow stopped. Residual renal urea clearance K_r (ml/min) was calculated from interdialytic urine collections, and ultrafiltration rates (Q_f, ml/min) were based on pre and post-treatment weights. For the historical cases (10-15), published data including C_0, C_1, C_{1eq}, and mid-treatment (C_s) BUNs, dialysis duration (T_d, min), K_d, Q_f, K_r, weight; and recirculation status [5, 6].

The VVDP perturbation solution is detailed in the appendix, where equation (9) predicts urea concentration as a function of time and the other model parameters. For the VVSP, FVDP, and VVDP models, estimates of V and G (K_d specified by the user) or K_d and G (V specified) are obtained by iterative methods, minimising the discrepancy between observed and predicted BUN as described in the appendix. Calculation of $K_d t$/V used blood water K_d, and protein catabolic rate (PCR) was calculated by the Borah equation (PCR = 0.262 * G + 0.294 * V, for G in μmol/min, V in liters, and PCR in g/day) and normalised to V/ 0.58 (nPCR) [12]. The errors associated with the various models are expressed relative to the reference values from the single pool analysis with measured K_d and *equilibrated* post-dialysis BUN (C_{1eq}). For both two pool models, intercompartmental urea mass transfer K_{ei} was assumed to be ~10 ml/min/kg [5, 6, 13]. and the ratio of extracellular to intracellular volume (V_e/V_i) at dry weight was assumed to be ~1/3 [14]. The Smye method predicts C_{1eq} based on intradialytic samples (C_0, C_s, C_1); the predicted value is then used with the VVSP to estimate

equilibrated parameters [6, 15]. The Daugirdas rate equation furnishes a semi-empiric estimate of equilibrated K_dt/V based on the standard single pool result and dialysis duration T_d [16].

For patients 2, 4, 7, 8, and 9, deemed to be in a clinical steady-state (no intercurrent illnesses and no dietary or dialysis prescription changes in the previous week), results of 2 BUN (steady-state) and 3 BUN sampling were formally compared as described in the appendix. Pre- and end-treatment BUNs were collected for a 2 week period (7 consecutive treatments for all but patient 9, in whom only 4 consecutive studies were obtained due to a schedule change). In addition, K_d, blood flow, and recirculation were measured at outset and used to establish urea volume V. Blood flow was verified with each treatment. For the retrospective analysis in Table 5, anthropometric estimates of total body water based on gender and height were supplied to estimate K_d [17].

DOQI advises that residual renal clearance be expressed as the *equivalent dialyzer clearance needed to replace K_r and maintain the same pre-dialysis BUN* [2]. In practice, it may be approximated by $(Kt/V)_{renal} = k\,K_r/V$, with $k = 5.5$ for thrice weekly dialysis and 6.5 for twice weekly dialysis (K_r in ml/min, V in liters) [18, 19]. To evaluate k in children modelled with the VVDP, we simulated symmetric dialysis schedules (3, 4, or 5 weekly treatments, for a total of 15h/week) in 4 typical pediatric scenarios (weights 15, 30, 45, 60 kg; $Q_f = 90$ ml/kg/week; $C_0 = 25$ mM; and $G = 3$ μmol/kg/min). K_d was then systematically varied from 2 - 5.5 ml/min/kg, and K_r was varied from 0-6 ml/min/1.73 m^2. Each value of k was calculated from 42-46 analyses, where K_r was set to zero and K_d adjusted to maintain the same pre-dialysis urea concentrations.

Data are mean ± 1 SD. All models were implemented with Mathematica 4.0 (Wolfram Research, Champagne, Ill) . For the VVSP and VVDP, a C language Add-In for Microsoft Excel (Redmond, Wa) is also freely available from the author (AS). Statistical analysis was performed using SAS 6.12 (SAS Institute, Durham, NC). Mean errors relative to reference values were compared by one way ANOVA, with significant group differences ($p < 0.05$) localised by post-hoc application of the pairwise Least

Significant Difference test. Confidence intervals on the discrepancy between different estimates of the same parameter are calculated as Bland-Altman 95% limits of agreement [20].

Results:

Figure 1 illustrates the error in estimation of true equilibrated $K_d t/V$ when the unequilibrated, end-dialysis BUN is used with the VVSP model. The 11 kinetic studies performed in our dialysis unit (treatment duration 283 ± 27 min) are compared to the 6 historical cases with a treatment duration of 142 ± 30 min. Despite different dialysis regimens, there is a comparable degree of overestimation in $K_d t/V$ in the two groups (0.22 ± 0.07, range 0.14 - 0.32, vs 0.21 ± 0.07, range 0.12 - 0.29, $p = 0.77$).

Reference ('true') values for K_d, V, and G were obtained by direct measurement of K_d with access recirculation excluded. K_d, in turn, furnishes equilibrated single pool estimates of V and G. As shown in fig. 2 (patient 9), these values may be used to generate predicted blood (ECF) or ICF urea profiles for the various models. During treatment, BUN predicted by the standard VVSP model is consistently higher than observed and fails to reproduce post-dialysis urea rebound. The FVDP model (not shown) also predicts higher than observed intradialytic BUN, particularly late in dialysis. As shown here, the VVDP model predicts both intercompartmental urea disequilibration and the post-treatment rebound phase, with a better fit to the observed data likely to yield improved parameter estimates.

Table 2 compares reference values from the equilibrated single pool model with estimates derived from the VVSP, FVDP, VVDP, Smye method and rate equation using standard pre- and end-treatment BUN. Both the unequilibrated VVSP and FVDP models significantly underestimated urea distribution volume V compared to the VVDP (-2.2 ± 3.6% body weight). The group difference was significant (ANOVA $p < 0.001$) and localised to the comparison of VVDP with VVSP (p=0.002) and FVDP (p<0.001). As a consequence, both the unequilibrated VVSP and FVDP models overestimated $K_d t/V$ to a comparable degree. When the Smye method was used to predict the equilibrated post-

treatment BUN, the mean K_dt/V error was less but the variability was higher, resulting in wider 95% limits of agreement. The rate equation and the VVDP model had similar smaller errors (-0.03 ± 0.06 vs. 0.06 ± 0.07) and narrower limits of agreement. Once again, ANOVA $p < 0.001$, and post-hoc comparisons confirmed that both the VVDP and rate equation errors were significantly smaller than the unequilibrated VVSP (p=0.002) and FVDP (p<0.001) results.

Without a second pre-dialysis BUN for the historical cases, estimation of urea generation (G) and protein catabolic (PCR) rates involved only the 11 studies performed in our unit. In both cases, the VVSP estimates were associated with a larger errors than the VVDP. For G, mean errors were, respectively, -8.4 ± 3.6 vs -2.6 ± 5.8 μmol/min (paired t, p=0.01). For PCR, errors were -2.9 ± 1.0 vs -0.8 ± 1.6 g/d (p=0.005). In the calculation of nPCR, underestimation of V by the VVSP will partially offset this error, with a mean discrepancy of 0.06 ± 0.05 g/kg/d compared to 0.02 ± 0.05 g/kg/d for the VVDP ($p = 0.09$).

Reproducibility of parameter estimates was assessed by sequential studies in 5 patients deemed to be in a clinical steady-state, with no intercurrent illness and no diet or dialysis schedule change in the previous week. Table 3 shows the intrasubject coefficient of variation (c.v.) for the two BUN (n=32) and three BUN (n=27) studies. The variation in modelled values of V, K_d and K_d t/V are ~ 5% or less by either method. Discrepancies between the two methods (mean ± SD) were small for V as a proportion of post-dialysis weight (0.2 ± 1.7%), whole blood K_d (-0.01 ± 0.02 ml/kg/min), and K_dt/V (-0.01 ± 0.07). For K_dt/V, the 95% agreement interval (based on 27 paired comparisons) was -0.15 to 0.13. Intrasubject variations in G and nPCR are larger, 12-14% for the 3 BUN method and 8-10% for the steady-state analysis. Since the two methods do not reflect the same interdialytic intervals, only average values of G and nPCR may meaningfully be compared [18], and moving averages (r=3) were calculated before assessing agreement. The discrepancy between methods was -0.9 ± 10.3 μmol/min for G and 0.0 ± 0.07 g/kg/d for nPCR, with 95% limits of agreement between -0.15 to 0.15 for the latter, based on 17 paired comparisons.

In practice, $(Kt/V)_{renal} \sim k \, K_r/V$, where k is determined by formal kinetic modelling based on the notion of equivalent dialyzer clearance needed to *replace* K_r and achieve the same pre-dialysis urea concentrations [2, 18, 19]. Table 4 displays k values obtained with the VVDP model as weight (15-60kg), K_d (2-5.5 ml/min/kg), K_r (0-6 ml/min/1.73 m^2), and weekly schedule (3-5 treatments/week) were systematically varied. For a given treatment frequency and dialyzer $K_d t/V$, the linear approximation continues to hold for the 2 pool model, with all $R^2 \geq 0.94$. As with the VVSP (not shown), there is a striking dependence on dialyzer clearance, with $k = 4.7$ when $K_d t/V = 1.0$ and $k = 9.1$ when $K_d t/V = 2.0$.

We retrospectively reanalysed 292 monthly studies collected on the 12 prepubertal patients described in our earlier report [1]. Our treatment regimen consisted of 14.8±1.8h per week of hemodialysis, thrice weekly except as noted in Table 5, and recommended nutritional intake (RNI) for energy and protein. The latter was achieved with supplements, gavage feeds, and intradialytic parenteral nutrition. Compared to RNI promoted by the American Dietetics Association for children on hemodialysis [21], mean intake was 91% for calories and 156% for protein. The urea reduction ratio (URR) was 84.7 ± 4.9%. Despite earlier reports associating obesity with attempts to supplement calories beyond 70-80% RNI [22], no overt obesity was observed by conventional criteria.

Table 5 compares the unequilibrated VVSP and VVDP estimates of dialyzer $K_d t/V$ (treatment^{-1}), normalised protein catabolic rate (g/kg/day), and modelled dialyzer clearance K_d (whole blood, ml/min/kg). All three kinetic parameters are significantly smaller in the two pool analysis (paired t, $p < 0.001$). Estimated $(Kt/V)_{renal}$ using the equivalence relationships defined in Table 4 is also shown. Total Kt/V (dialyzer + residual renal, treatment^{-1}) was 2.10 ± 0.35 (range 1.48 - 2.73) for the VVSP model vs. 1.95 ± 0.34 for the VVDP (range 1.34 - 2.53, $p < 0.001$). The delivered (modelled) K_d was 4.4 ± 0.9 ml/min/kg (VVDP) vs. 4.8 ± 0.9 (VVSP, p<0.001), and nPCR was 1.52 ± 0.38 (range 0.9 - 2.2 g/kg/day).

Discussion:

Urea is regarded as a surrogate marker for small, dialyzable toxins derived from protein metabolism. In isolation, blood concentrations are poor outcome predictors [23]. However, *for a given protein catabolic rate* (≈ steady-state protein intake)*,* the National Co-operative Dialysis Study (NCDS) identified time averaged urea concentration (TAC) as the most powerful predictor of treatment failure (death or hospitalisation) [24, 25]. Time on dialysis - a surrogate for clearance of 'middle molecules' whose elimination is less responsive to increased flow rates - was a significant but less powerful discriminator (hospitalisation) [26]. A 'mechanistic' re-analysis of the NCDS data introduced urea $K_d t/V$, the number of times the total body water was cleared of urea per treatment and a measure of *delivered* dialysis dose when derived from kinetic modelling [27]. Prospective trials have subsequently confirmed the relationship between $K_d t/V$ and uremic symptoms, particularly anorexia [28], and urea kinetics are widely used to identify discrepancies between delivered and prescribed HD dose [29, 30]. More recently, it has been suggested that $K_d t/V$ in the range not examined by the NCDS might further reduce mortality [31], prompting an controlled randomised trial with single pool $K_d t/V$ 1.2 vs 1.6 [32].

Comparable data in children is lacking. Concern about applicability of the NCDS definition of adequacy to children is one issue. The pediatric literature has emphasised age-appropriate outcome measures, particularly growth and development [3, 22, 33]. There has also been long-standing concern with overestimation of dialysis dose in children by the standard VVSP model, which cannot account for the compartmental effects illustrated in Fig. 2 [4, 5, 6, 7] . More complex models have proven useful for investigational purposes, but lack of closed-form solutions and the number of parameters requiring *a priori* estimates make them less practical in a clinical setting [34]. There have been several ingenious approaches to closed-form solutions that reflect the multicompartmental nature of urea distribution and are more suitable for iterative curve fitting. The FVDP model also spuriously inflates apparent dialyzer clearance. Smye adapted it with his prediction formula for the equilibrated post-treatment BUN based on intradialytic samples [6]. It requires an additional BUN mid-

treatment, precluding analysis of previously collected studies, and the resulting estimate has a wide confidence interval, confirming a recent pediatric comparison [35].

Unlike this series arrangement of ICF and ECF compartments, an alternate model with 2 parallel pools has also been proposed, in which urea sequestration occurs in poorly perfused organs, such as bone, skin and muscle [16, 36]. The two approaches are mathematically equivalent, with K_{ei} replaced by Q_L, the fraction of cardiac output to the low perfusion compartment [37]. The model predicts that K_dt/V overestimation will be aggravated by shorter treatment duration (T_d) and increased dialysis efficiency (K_d/V). Consequently, the rate equation estimates equilibrated K_dt/V from the standard single pool result and T_d. As shown here and in the comparison by Marsenic *et al* [35], this semi-empiric approximation furnishes an excellent estimate of equilibrated K_dt/V in pediatric HD. Although the rate equation predicts that overestimation of K_dt/V by the VVSP model will diminish as treatment is prolonged, the absolute error in our patients with almost 5h of dialysis is comparable to that observed in the cases dialyzing for half as long and is likely to be clinically significant in some (range 0.14-0.32).

The proposed VVDP model is highly idealised, and the solution in eq. (9) is an approximate one. Still, it accurately predicts observed blood urea concentrations and reproduces the key treatment-induced compartmental effects. This good fit with observed data permits reliable estimates of equilibrated kinetic parameters using standard pre- and end-dialysis BUNs. Although it neglects osmotic flux, sodium ramping between 140-150 mM in our unit did not appear to influence the goodness of fit. It is also parsimonious in terms of additional parameters requiring *a priori* estimates, with only 2 beyond those of the VVSP: i) whole body urea mass transfer coefficient $K_{ei,}$ and ii) the ratio of ECF to ICF volume at dry weight. In adults, the former is ~ 800 ml/min/1.73 m^2 (reviewed in [13]) Similar values have been reported from careful analysis of urea rebound in 6 pediatric patients [5, 6]. For the latter, we adopt a value of 1/ 3 [14].

The intrasubject variation in kinetic parameters in Table 3 is similar to the results of single pool modelling in children [38]. This reproducibility of V/Wt is of clinical utility: Current practice in our dialysis unit is to measure K_d and recirculation fraction concurrently in 3 different treatments. The measured clearance may be corrected for access recirculation with equation (3). Measured K_d is then used with the VVDP model to estimate V, with its mean value used to fit K_d in subsequent studies. Alternatively, the physician may estimate K_d based on flow rates and measured dialyzer urea mass transfer K_oA [2]. This can be used to fit V, with changes in the latter from baseline identifying technical problems with dialysis. The two approaches are equivalent, and we prefer to interpret K_d directly. K_dt/V is largely unaffected by this choice, since errors in K_d and V tend to be proportional,.

In adults, abbreviated 2 BUN (steady-state) sampling may be preferable to the 3 BUN method, since it is more easily performed, less dependent on a single interdialytic interval, and less prone to patient manipulation of a study in progress [39]. As shown here, the two methods produce virtually identical estimates for V, K_d and $K_d t/V$. This is not unexpected, since V and K_d are principally determined by the intradialytic urea samples, while G and nPCR largely reflect the interdialytic kinetics. By reflecting protein balance for the whole week, the steady-state method is theoretically less prone to dietary indiscretions in the single interdialytic interval spanned by the 3 BUN samples. The smaller coefficient of variation for the steady-state estimates of G and nPCR suggest that this is equally true in children. Because of study-to-study variability, it is important to consider only mean values for G and nPCR from repeat studies when making prescription changes. With this proviso, agreement between the two methods was again satisfactory, although the 3 BUN method is the only option when the steady-state assumption does not hold.

The notion of equivalence used to define the contribution of residual renal clearance $(Kt/V)_{renal}$ in terms of dialyzer clearance required to *replace* it and achieve the same blood urea concentrations is widely recognised. It is based on the NCDS conclusion that, for a given protein catabolic rate, blood urea concentration is the most important predictor of outcome [2, 18, 19, 25]. Although there is little

comparable pediatric data, measuring renal clearance consistently is a prerequisite for carrying out such studies. An approximation scheme ($k\,K_r/V$, $k = 5.5$ for thrice weekly dialysis) also appears reasonable for what is, after all, a rough estimate. As with the single pool model in adults, k varies with both dialysis frequency and achieved K_dt/V, since lower post-treatment BUN permits the same residual renal function to maintain lower blood urea concentrations. The tabulated results may also be used with the single pool model or rate equation estimates where target K_dt/V exceeds 1.1 or where fluid and other considerations mandate a more frequent dialysis schedule.

Given the paucity of pediatric data relating outcome to delivered dialysis dose, reanalysis of our prepubertal cohort was thought warranted, to furnish a better estimate of the dialysis dose needed to sustain normal growth. Even if the NCDS experience can be extrapolated directly to uniquely pediatric manifestations of uremia, their recommendations were based on a protein intake of ≤1.1 g/kg/d, which represented an inflection point on the therapy target modelling line. Above this, the target line begins to cross Kt/V isopleths in an upward direction [27], an important consideration given current guidelines from the American Dietetics Association for children on hemodialysis (ranging from 3.3 g/kg/day for infants to 1.3-1.5 g/kg/day in teenagers) [1, 21]. Even though anabolism in growing children will contribute to a discrepancy between dietary protein intake and protein catabolic rate, this is small (~ 0.05 g/kg/d) even during periods of rapid growth [40, 41]. As these kinetic studies confirm, protein *catabolism* exceeded the NCDS standard (nPCR 1.52 ± 0.38, range 0.9 - 2.2 g/kg/day), and increased dialysis requirements might therefore be expected.

The K_dt/V estimate provided by the VVDP model moves our dose targets closer to the norm, but the combined Kt/V (1.95 ± 0.34, range 1.3-2.5) continues to exceed current guidelines. Although we attempt to maximise blood flow and dialyzer surface area, actual dialyzer clearance (4.4 ± 0.8 ml/min/kg) is considered conventional [41, 42], not unexpected given practical limitations in pediatric access flows and maximally tolerated extracorporeal volumes. There is in fact little experience with high flow ('high flux') hemodialysis in children [43], leaving time on dialysis as the principle means of

augmenting clearance. We are reluctant to extrapolate our results to shorter treatment times, where small solute K_dt/V is maintained by higher flows. This approach may compromise membrane-limited middle molecule clearance, which is minimally responsive to changes in flow rates. For a given TAC/PCR, time on dialysis (a surrogate measure of middle molecule clearance) was a significant predictor of morbidity in the NCDS, albeit less powerful than TAC [26, 44]. The relatively short follow-up (6 mo) also precluded appreciation of longer-term middle molecule toxicity. Moreover, the role of middle molecules in the pathogenesis of growth failure in children is not known.

We believe the experience at our center supports an upward revision in dose guidelines for children. However, a multicenter, controlled trial should address this question prospectively and more clearly define treatment targets for various ages and subsets . We hope our results and the kinetic model developed and validated here will provide a starting point for such discussions.

Appendix:

A convenient closed-form solution is not available for the variable volume, two pool (VVDP) model illustrated in Figure 3 (see caption for definition of variables). Although digital computers and numeric integration permit investigation of more realistic models [34, 45], this process is computationally intensive and time consuming, not ideally suited to the routine estimation of model parameters by iterative curve fitting, particularly in a clinical setting. For this particular application, we therefore seek an *approximate* closed-form solution - an expression for blood urea concentration as a function of time and other model parameters - based on the Wentzel-Kramer-Brillouin (WKB) method [46]. Like all perturbation schemes, it relies on identification of a 'small' parameter ε, where the case $\varepsilon = 0$ permits an exact (*unperturbed*) solution. To this simpler model is added a correction (*perturbation*), typically derived from the first few (for $\varepsilon < 1$, the largest) elements in a power series with terms in ε^0, ε^1, ε^2… etc, as in equation (7) below [10].

Assumptions: The following explicit assumptions underlie this derivation.

a) Total body water is divided into well-mixed intracellular (ICF) and extracellular (ECF) fluid compartments, separated by a barrier of *finite* urea mass transfer K_{ei} (~ 800 ml/min/1.73 m^2). A constant fraction *f* of Q_f = ultrafiltrate (and interdialytic weight gain) is attributed to the ICF.

b) Between dialyses, $K_d = 0$ and $Q_f < 0$. Otherwise, G, K_r, K_d, and Q_f are assumed to be constant, > 0, and confined to the ECF. Urea elimination in the dialyzer and native kidney is described by first order processes i.e. $\cong (K_d + K_r) C_e$.

c) The effect of access recirculation on dialyzer clearance is formally treated here, but cardiopulmonary recirculation is not, although it is amenable to similar analysis for patients with AV fistulae [47].

d) From the 292 kinetic studies analysed for Table 5, the normalised ultrafiltration rate $q_f = Q_f /(K_d+K_r)$ = 0.03 $\pm$ 0.02 (range 0.00 - 0.09). The product fq_f that appears in the scaled equations (5) may therefore be considered a second-order effect and neglected as long as *f* is small. During dialysis,

both whole body and segmental bioimpedance data puts the slope of the extracellular vs total ultrafiltrate relationship close to unity (i.e. $f \sim 0$) [48, 49]. Similar data have been used to justify this assumption - essentially, constant ICF volume - in other multicompartment models, at least as a first order approximation [45, 50]. We assume this also applies for the interdialytic interval.

e) We will identify $\varepsilon = (K_d + K_r)/K_{ei}$ as the 'small' parameter for the perturbation expansion. Off dialysis, this is certainly true. On dialysis, we requires blood water $K_d \ll K_{ei}$. In adults, $K_{ei} \sim 800$ ml/min/1.73 m^2 (reviewed in [13]). Pediatric data is more limited, although Smye et al assumed that $K_d/K_{ei} < 0.4$ in the derivation of their fixed volume model. Based on their analysis of rebound kinetics in 6 pediatric patients, we have assumed $K_{ei} \sim 10$ ml/kg/min for clinical applications [5, 6], with typical whole blood clearances of 3-4 ml/kg/min [41, 42] and blood water $K_d \sim 90\%$ of these values.

Derivation: Dialyzer clearance includes both diffusive and convective urea flux, given by

(1)

$$\frac{Q_{bi} \, C_{bi} - Q_{bo} \, C_{bo}}{C_{bi}} = \frac{Q_{bi} \, (C_{bi} - C_{bo})}{C_{bi}} + \frac{Q_f \, C_{bo}}{C_{bi}}$$

In the event of access recirculation, *effective* clearance is obtained by replacing Q_{bi} and C_{bi} with Q_p and C_p, respectively. Blood flow continuity ($Q_{bi} = Q_p + Q_r$) and urea mass conservation ($C_{bi} Q_{bi} = C_p Q_p + C_{bo} Q_r$) may be invoked to calculate the recirculation fraction: $Q_r/Q_b = F_r = (C_p - C_{bi})/(C_p - C_{bo})$ (2). If this fraction is known, it follows from (1) and (2) that the measured clearance K_d may be used to estimate effective clearance K_{de} [50, 51]:

(3)

$$K_{de} = \frac{K_d \, (1 - F_r)}{1 - F_r \left(1 - \frac{K_d}{Q_{bi}}\right)}$$

If modelled (effective) K_d differs significantly from expected K_d, (3) may also be rearranged to calculate the recirculation fraction on the basis of this discrepancy. Mass balance considerations then lead to the following governing equations, where square brackets denote function arguments (e.g. $y = h[x]$), ∂_t indicates the time derivative, and K_d refers to *effective* dialyzer clearance:

(4)

$$\partial_t \ (C_i[t] \ V_i[t]) \ = \ K_{ei} \ (C_e[t] \ - \ C_i[t]) \ - \ f \ Q_f \ C_i[t]$$
$$\partial_t \ V_i[\tau] \ = \ -f \ Q_f$$
$$\partial_t \ (C_e[t] \ V_e[t]) \ = \ G \ - \ (K_d \ + \ K_r) \ C_e[t] \ - \ K_{ei} \ (C_e[t] \ - \ C_i[t]) \ + \ f \ Q_f \ C_i[t]$$
$$\partial_t \ V_e[\tau] \ = \ - \ (1 \ - \ f) \ Q_f$$

To identify parameters that are *small independent of the choice of units*, (4) must first be made non-dimensional by appropriate scaling factors [52]. It is convenient to scale concentrations by $C_0 = C_e[0]$, volumes by $V_0 = V_e[0]$, and express time in units of $T_0 = V_e[0] \ / \ (K_d + K_r)$. Between dialyses, the choice of time scale requires $K_r \neq 0$, accommodated in practice by fixing a minimum non-zero value. The volume and time scales also imply that K_{ei}, Q_f and other clearance terms are scaled by $K = K_d + K_r$. Integrating (4b) and (4d) directly and applying these scales, *with lower case names representing scaled non-dimensional variables and scaled time denoted by* τ, (4) becomes:

(5)

$$c_i'[\tau] \ = \ \frac{k_{ei} \ (c_e[\tau] \ - \ c_i[\tau])}{v_i[0] \ - \ f \ q_f \ \tau}$$

$$v_i[\tau] \ = \ v_i[0] \ - \ f \ q_f \ \tau$$

$$c_e'[\tau] \ = \ \frac{\frac{g}{c_0 \ v_0} \ - \ (1 \ + \ k_{ei} \ - \ q_f \ + \ f \ q_f) \ c_e[\tau] \ + \ (k_{ei} \ + \ f \ q_f) \ c_i[\tau]}{1 \ - \ q_f \ \tau \ + \ f \ q_f \ \tau}$$

$$v_e[\tau] \ = \ 1 \ - \ q_f \ \tau \ + \ f \ q_f \ \tau$$

As outlined in *assumption (d)*, $fq_f \ll 1$. With this, (5) may be converted to an equivalent second-order equation by separately eliminating $c_i[t]$ and $c_e[t]$. Urea disposition in both compartments is then described by:

(6)

$$(1 \ - \ q_f) \ c[\tau] \ + \ \left(1 \ - \ q_f \ \tau \ + \ v_i \ + \ \frac{v_i}{k_{ei}} \ - \ \alpha \ \frac{q_f \ v_i}{k_{ei}}\right) c'[\tau] \ + \ \left(\frac{v_i}{k_{ei}} \ - \ \frac{q_f \ \tau \ v_i}{k_{ei}}\right) c''[\tau] \ = \ \frac{g}{C_0 \ V_0}$$

with $\alpha = 1$ for $c_i[t]$ and $\alpha = 2$ for $c_e[t]$. The WKB method was originally developed to approximate solutions to the Schrödinger equation, which - like (6) - is a linear, inhomogenous ($g \neq 0$), second order differential equation with time varying coefficients [46]. Linearity ensures that the general solution of (6) is given by the solution to the homogenous equation ($g = 0$) *plus* any particular solution to the inhomogenous equation. Direct substitution of the steady-state concentration $C_{ss} = G/(K_d + K_r - Q_f)$ (in non-dimensional units, $g/ \ (V_0 \ C_0 \ (1-q_f))$) will verify that it is a particular solution. Without loss of generality, we therefore apply the WKB approximation to the homogenous case.

We identify $\varepsilon = 1/k_{ei} = (K_d + K_r) / K_{ei}$ as a 'small' parameter for the perturbation expansion (see *assumption (e)*). Essentially, the WKB method imposes on (6) a solution of the following form, where $\delta = \varepsilon^j$ and $S[\tau]$ is a function of both τ and δ expanded as a power series in δ:

(7)

$$e^{\delta^{-1} \sum_{i=0}^{\infty} S_i[\tau]\, \delta^i}$$

To determine the form of δ, we substitute (7) in (6) and first consider only those terms that are retained in the limit $\delta \to 0$. By dominant balance [46], (6) is seen to hold only if $\delta = \varepsilon$. With this result, the substitution is repeated, this time retaining all terms, and coefficients of successive powers of ε are collected. When individually equated to zero, these yield a series of ordinary differential equations to be solved sequentially for $S_i[\tau]$. We consider here only the first-order approximation; since our goal is parameter estimation from observed blood urea concentrations, the utility of this approximation will be measured by goodness of fit to experimental data.

(8)

$$(1 - q_f\, \tau + v_i)\, S_0'[\tau] + (1 - q_f\, \tau)\, v_i\, S_0'[\tau]^2 = 0$$
$$1 - q_f + v_i\, (1 - \alpha)\, S_0'[\tau] + (1 - q_f\, \tau)\, v_i\, S_0''[\tau] + (1 - q_f\, \tau + v_i)\, S_1'[\tau] + 2\, (1 - q_f\, \tau)\, v_i\, S_1'[\tau]\, S_0'[\tau] = 0$$

Equation (8a) has two solutions for $S_0[\tau]$, each of which yields a distinct solution for $S_1[\tau]$ when substituted in (8b). These provide two independent solutions to (6) of the form specified by (7). By virtue of linearity, the general solution is a superposition of these individual terms, restored to the original units and added to the particular solution of the inhomogenous equation to yield the following result:

(9)

$$C_\alpha[t] = C_{ss} + k_1 \left(\frac{V_t[0] - Q_f\, t}{V_t[0]} \right)^{\frac{K_d + K_r - Q_f}{Q_f}} + k_2\, e^{-\frac{K_{ei}\, t}{V_i}} \left(\frac{V_e[0] - Q_f\, t}{V_e[0]} \right)^{\frac{K_d + K_{ei} + K_r - (\alpha-1)\, Q_f}{Q_f}} \left(\frac{V_t[0]}{V_t[0] - Q_f\, t} \right)^{\frac{K_d + K_r}{Q_f}}$$

where $V_t[0] = V_e[0] + V_i$, $\alpha = 1$ for $C_i[t]$, and $\alpha = 2$ for $C_e[t]$. The k_i are constants of integration determined by imposing appropriate initial conditions on (9). For the treatment interval, these conditions are $C_e[0] = C_i[0] = C_0$, with the derivatives at t=0 specified by (4a) and (4c), respectively: $C_i'[0] = 0$ and $C_e'[0] = (G - C_0\, (K_d + K_r - Q_f))/ V_e[0]$. Substitution in (9) and straightforward, if tedious, algebra yields the required integration constants:

(10)

$$k_1 = k_0 - k_2$$

$$k_2 = \frac{(G - C_0\,(K - Q_f))\,V_i\,V_x}{V_i\,(Q_f\,V_x \pm K\,(V_i - V_e[0])) \pm K_{ei}\,V_t[0]^2}$$

where $k_0 = C_0 - C_{ss}$ and $K = K_d + K_r$. For $C_i[t]$, $V_x = V_e[0]$ and the $\pm$ terms in the denominator are added; for $C_e[t]$, $V_x = V_i$ and the denominator terms are subtracted. For both pools, in the limit $K_{ei} \to \infty$ (i.e. $\varepsilon \to 0$), $k_2 \to 0$, $k_1 \to k_0$, and (9) reduces identically to the standard VVSP result, the unperturbed model for this particular expansion [18]. The perturbation term (multiplying k_2) incorporates the effects of finite intercompartmental urea mass transfer K_{ei}, characterised by exponential decay with time constant $-K_{ei}t/V_i$. The k_i for the post-dialysis ECF (not shown) may be derived in an analogous fashion by imposing appropriate initial conditions on (9): At the end of dialysis, $C_e[0] \neq C_i[0]$, and numeric values are furnished by the intradialytic equations, with Ce'[0] from (4c).

Iterative parameter estimates: These results are used to determine unknowns K_d, V, or G by minimising the error between predicted and observed ECF urea concentrations, here with Brent's conjugate gradient method in one dimension [53]. Using either (9) or the standard VVSP or FVDP prediction formulae (for the latter, eq 5.3-4 in [9]), the same algorithm is used to fit V to C_0 and C_1 (intradialytic) with K_d measured and G ~ 3 μmol/kg/min. Alternatively, K_d may be estimated if V is specified from previous kinetic studies or anthropometric formulae. This value is then used with C_1 and C_2 (interdialytic) to calculate G, in turn used to refine the estimate of V (or K_d), and the process iterated until convergence ($\pm 1\%$). In a steady-state, C_2 may be omitted, and G fit instead to the assumption that pre-dialysis BUN equals C_0 at the same point in the previous (or next) weekly cycle, producing estimates of G and protein catabolic rate that reflect protein balance during the entire week instead of the single interdialytic interval spanned by C_1 and C_2. For the two pool analyses, the only additional parameters requiring *a priori* estimates are K_{ei} and the ratio of V_e/V_i at post-dialysis 'dry' weight. Sensitivity analysis (not shown) demonstrates that the resulting predictions are relatively insensitive to imprecision in these estimates.

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Tables: ⑦

Clinical data and abbreviated BUN profiles from 17 equilibrated kinetic studies used for validation of the variable volume, two compartment model. *Abbreviations*: pre (C_0), post- (C_1), and equilibrated (C_{1eq}) BUNs (mM, whole blood); dialysis duration (T_d, min); measured dialyzer clearance K_d (ml/min, whole blood); ultrafiltration rate (Q_f, ml/min); residual renal urea clearance (K_r, ml/min); weight (post-dialysis, kg)

Patient	Weight	Q_f	T_d	C_0	C_1	C_{1eq}	K_d	K_r
1	30.6	1.3	300	13.1	1.5	1.8	176	0.0
	30.8	5.1	294	29.8	3.0	3.8	178	0.0
2	46.0	2.0	300	15.7	2.4	2.9	181	0.0
	44.6	3.7	300	18.5	3.1	3.8	180	0.0
3	66.8	0.8	240	12.5	2.9	3.3	217	9.0
4	50.4	5.3	300	12.2	1.7	2.1	201	0.0
5	18.0	0.4	240	18.8	8.2	9.2	37	3.8
6	36.1	5.8	240	14.1	3.1	3.5	208	1.6
7	65.0	7.3	300	21.5	5.0	5.4	233	3.4
8	34.0	5.0	300	21.4	2.4	2.8	206	0.0
9	30.2	4.0	300	34.6	3.9	4.7	181	0.0
10	15.0	1.7	173	10.7	3.3	3.8	72	0.0
11	31.2	4.9	182	10.9	4.3	5.3	101	1.6
12	18.8	1.9	105	7.4	4.3	4.7	61	0.6
13	11.2	0.8	126	6.3	2.1	2.4	61	0.0
14	24.3	4.3	140	13.6	5.7	6.7	102	0.6
15	21.7	4.9	123	8.2	3.9	4.8	89	0.0

	$VVSP_{eq}$	*Error*	*VVSP*	*FVDP*	*Smye*	*VVDP*	*Rate*
V/Wt %	59.7±7.5	*mean*	-8.2 ± 4.2	-9.1 ± 3.0	-4.5 ± 8.5	-2.2 ± 3.6	
		95% limits	-16.4–0	-15–3.1	-21.1–12.1	-9.2–4.8	
$K_d t/V$	1.57±0.68	*mean*	0.22 ± 0.07	0.29±0.17	0.11±0.26	0.06±0.07	-0.03±0.06
		95% limits	0.09–0.35	-0.04–0.62	-0.39–0.62	-0.08–0.19	-0.16–0.10

Table 3:.

Comparison of 2 BUN (steady-state) and 3 BUN kinetic studies: Reproducibility is reported as intrasubject coefficient of variation (cv, %). Bland-Altman 95% limits of agreement are calculated on the discrepancies between the two methods. *Abbreviations:* V/Wt = urea distribution volume as fraction of post-dialysis weight (%); K_d = whole blood dialyzer clearance (modelled) ml/min/kg; K_dt/V = treatment^{-1}, G = urea generation rate (μmol/min), nPCR = normalised protein catabolic rate (g/kg/day)

	V/ Wt %	*K_d ml/min/kg*	*K_d t/V*	*G μmol/min*	*nPCR g/kg/d*
Mean ± SD	61.9 ± 9.6	4.5 ± 0.3	2.21 ± 0.43	161 ± 44	1.14 ± 0.43
two BUN cv %	5.7±2.1	3.3 ± 0.8	5.4±2.1	8.4±3.8	9.5±2.6
three BUN cv %	5.2±1.0	3.4 ± 0.7	5.6±2.4	13.8±2.7	12.3±2.5
95% limits	-3.0–3.5	-0.03–0.06	-0.15–0.13	-19–21	-0.15–0.15

Table 4:

Proportionality constant for estimation of $(Kt/V)_{renal} = k\,K_r/V$ as a function of dialysis frequency and dialyzer clearance (K_r in ml/min, V in liters). Each k value is based on 42-46 simulations.

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$K_d t/V$	3x/wk	4x/wk	5x/wk
0.6			1.9
0.8		2.8	2.0
1.0	4.7	3.0	2.0
1.2	5.2	3.2	2.1
1.4	5.9	3.4	2.3
1.6	6.9	3.7	
1.8	7.3	4.1	
2.0	9.1	4.6	

Patients characterised as well-dialyzed based on growth rates : Monthly kinetic studies (n=292) from 12 patients previously characterised as well dialyzed based on normal growth rates and pubertal development (mean follow-up 26 mo). Dialysis was thrice weekly except as noted, with the mean number of weekly treatments during the study period indicated by: [a]3.6, [b]4.3, [c]3.2. Asterisks denote $p < 0.001$ (paired t, VVSP vs VVDP). Abbreviations: age = years at start of HD; ΔHSDS = mean annual change in height standard deviations score; URR = urea reduction ratio; sp = VVSP; dp = VVDP; nPCR= g/kg/day; K_d = whole blood ml/min/kg (modelled); K_d t/V = treatment^{-1}, $(Kt/V)_{renal}$ = renal Kt/V as equivalent dialyzer clearance from table 4.

Patient	Age	ΔHSDS/yr	URR %	$(K_dt/V)_{sp}$	$nPCR_{sp}$	$(K_d)_{sp}$	$(K_dt/V)_{dp}$	$nPCR_{dp}$	$(K_d)_{dp}$	$(Kt/V)_{renal}$
1[a]	5	1.42	86.8	2.00	2.00	5.8	1.83	1.92	5.2	0.18
2	12	0.50	77.7	1.48	1.28	4.2	1.34	1.24	3.8	0.95
3	14	0.25	80.4	1.55	0.94	4.0	1.42	0.90	3.7	0.18
4	5	0.16	85.8	2.12	1.54	4.8	1.97	1.50	4.5	0.00
5	10	0.52	84.0	1.77	1.78	4.0	1.65	1.73	3.7	0.56
6	5	0.41	85.1	1.80	1.26	5.1	1.63	1.21	4.6	0.21
7[b]	5	0.00	92.9	2.60	2.27	6.8	2.40	2.24	6.3	0.10
8[c]	7/12	0.05	91.4	2.25	1.50	5.4	2.08	1.48	5.0	0.00
9	10	-0.32	88.4	2.24	1.80	5.5	2.07	1.74	5.0	0.03
10	12	0.41	85.1	1.92	1.58	4.2	1.80	1.54	3.9	0.00
11	7	0.37	81.7	1.70	1.76	3.8	1.59	1.71	3.6	0.00
12	12	-0.04	77.1	1.48	1.06	4.3	1.34	1.01	3.9	0.00
mean		0.31±0.43	84.7±4.9	1.91±0.35	1.56±0.39	4.8±0.9	1.76±0.33 *	1.52±0.38 *	4.4±0.8 *	0.18±0.29

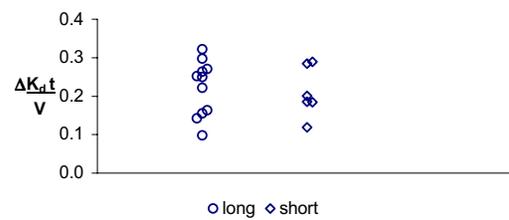## *Figures:*

K_dt/V error and dialysis duration:

$\Delta K_dt/V$ = error due to unequilibrated single pool analysis. Long treatment duration (n=11) was 283 ± 27 min, compared to 6 historical controls dialyzing for 142 ± 30 min.

**Figure 1:** *K_dt/V error and dialysis duration*

(patient 9) using measured K_d with equilibrated single pool ('true') urea distribution volume and urea generation rate. Actual BUN (●) was sampled at the dialyzer inlet during treatment, with an equilibrated peripheral sample drawn 1h post-dialysis. VVSP = variable volume, single pool model, VVDP = variable volume, double pool model, C_i= intracellular urea (mM), C_e = extracellular urea (mM).


Figure 2: *Predicted blood and intracellular urea concentrations*
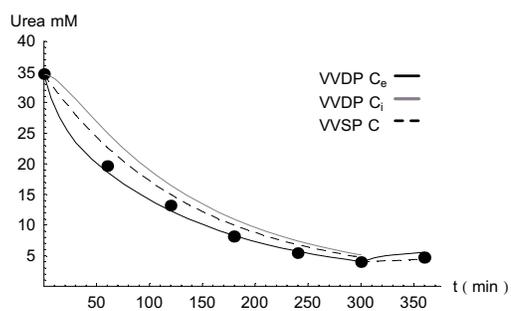
Figure 3: *Variable volume, two compartment urea kinetic model*

Abbreviations: V_i = intracellular fluid (ICF) volume, C_i = ICF urea concentration, V_e = extracellular fluid (ECF) volume, C_e = ECF urea concentration, K_{ei} = intercompartmental urea mass transfer coefficient, f = fraction of ultrafiltrate from ICF, K_r = residual renal urea clearance, G = urea generation rate, Q_f = ultrafiltration rate (> 0) or interdialytic weight gain (< 0), K_d = dialyzer urea clearance. In the dialyzer-access circuit, flows (Q) and concentrations (C) refer to peripheral blood (p), dialyzer inlet (bi), dialyzer outlet (bo), and access recirculation (r). Concentrations, flows, and K_d here refer to blood water (whole blood C / 0.93, 0.9·whole blood Q or K_d).

Figure 3: *Variable volume, two compartment urea kinetic model*
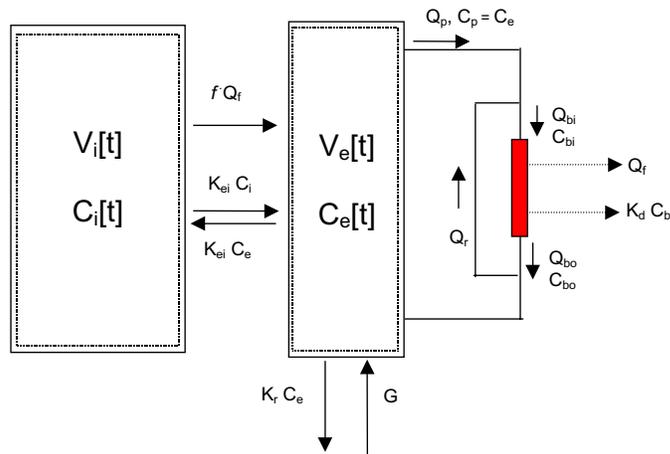
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