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Delivered clearance and timed concentrations for methanol dialysis duration in a simulation study

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Research Article

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Abstract

Background

Methanol dialysis-duration estimates may benefit from observed delivery and timed concentrations, but their incremental value over conservative fixed prescriptions is uncertain.

Methods

We compared 17 policies in 5,000 sessions per scenario across 18 scenarios. Latent truth was separated from observable inputs. Fixed comparators included a seven-target frontier and constant extensions calibrated on separate timing simulations. HYBRID-95 required both nominal integral and two-level criteria. Exploratory additions examined duration tails, assay delays and 20,000 additional primary sessions with unchanged calibration constants.

Results

In the original primary sample, HYBRID-95 produced 1/4,999 threshold exceedances (≥ 20 mg/dL; 0.02%), versus 1.14% for its calibrated fixed timer, both at median 8.25 hours. Hybrid minus fixed paired mean duration was 9.5 minutes; completed-session 95th percentiles were 13.25 versus 11.50 hours. The additional sample produced 2/20,000 hybrid exceedances (0.010%; Wilson interval 0.003–0.036%), versus 1.32% for the fixed timer, again at equal medians. Combined mapping-volume bias and later delivery loss caused 24.85% hybrid exceedance and 54 additional horizon overruns in the original stress scenario.

Conclusions

Combining observations improved simulated concentration outcomes at comparable median duration, with additional mean and upper-tail treatment burden. Systematic errors remained failure modes. Empirical calibration and independent review are required before clinical evaluation.

Background

Methanol hemodialysis duration depends on both toxin kinetics and clinical recovery. The Extracorporeal Treatments in Poisoning workgroup (EXTRIP) recommends considering termination when methanol is below 20 mg/dL and clinical improvement is observed, with alcohol dehydrogenase inhibition maintained during treatment.[1] Formate is the principal toxic metabolite, and its kinetics need not track those of the parent alcohol.[2] Persistent anion-gap acidosis, evolving visual toxicity or absent clinical improvement may therefore supersede a modeled methanol endpoint.

Hirsch and colleagues proposed a duration estimate using total body water and a fraction of manufacturer-specified urea clearance; a subsequent series evaluated that approach.[3, 4] Lachance and colleagues developed sex-specific prescriptions for high-efficiency hemodialysis.[5] Fixed prescriptions cannot anticipate all changes in delivered clearance. Ionic dialysance provides repeated estimates of urea-equivalent delivery, although its relationship to systemic clearance depends on measurement technique and recirculation.[6, 7]

Log-linear methanol analysis and time-weighted clearance have already been applied to a published case. [8] However, it remains unclear whether observed dialysis delivery provides useful information beyond simply extending a fixed dialysis prescription, especially when delivery estimates are uncertain. It is also unclear whether combining delivered-clearance information with timed methanol concentrations can compensate for the distinct failure modes of either approach alone. We therefore developed an observable-input simulation framework that incorporates measurement uncertainty and compared delivery-based, concentration-based, and combined criteria against conservative fixed prescriptions, including duration-matched comparators.

Methods

Design and information available to the policies

The analysis comprised 5,000 evaluation sessions for each of 18 scenarios and 5,000 separate calibration sessions per scenario. A timestamped analysis plan was frozen before the new runs, in accordance with simulation-reporting principles. [9] It was developed following an earlier development analysis and was not preregistered. No new human-participant or animal data were collected; ethics approval and consent were not applicable.

The generator retained a well-mixed, constant-volume compartment, adequate alcohol dehydrogenase blockade, and no ongoing absorption or endogenous elimination. Estimated volume was calculated using the Watson equations.[10] True volume, initial concentration, and methanol clearance were separated from estimated volume, measured concentrations, and observed dialysance. Policy functions accepted only an observable-data structure; latent quantities were supplied separately to the outcome evaluator. Figure 1 shows the information flow.

Integral and concentration projection

For true methanol clearance k(t) in mL/min and distribution volume V in mL, the underlying concentration model was:

$$\mathrm{C_t} \;=\; \mathrm{C_0}\,\exp\!\left[-\frac{1}{\mathrm{V_{mL}}}\int \mathrm{k}(\tau)\,\mathrm{d}\tau\right]$$

1

The estimated normalized dose was $\hat{Q} = \hat{\alpha}\Sigma D_i \Delta t_i / \hat{V}$, where D_i is observed ionic dialysance and $\hat{\alpha}$ maps it to methanol clearance. Volumes entered in L were multiplied by 1,000. The common model target was 16 mg/dL, distinct from the ≥ 20 mg/dL outcome threshold. The assumed post-cessation increase was r* = 0.08. Neither this fraction nor its later variability scenarios is an empirically calibrated rebound model.[11]

$$\hat{l} \;=\; \ln\left(C_{0,\mathrm{obs}}\right) \;+\; \ln(1 \;+\; r^{*}) \;-\; \widehat{Q}\,; \quad U \;=\; \exp(\hat{l} \;+\; z s_{l})$$

2

$$s_{l}^{2} \;=\; s_{C}^{2} \;+\; \widehat{Q}^{2}\left(s_{V}^{2} \;+\; s_{\alpha}^{2} \;+\; s_{\mathrm{cal}}^{2}\right) \;+\; CV_{D}^{2}\,\Sigma\,\left(\frac{\widehat{\alpha}\; D_i\;\Delta\; t_i}{\widehat{V}_{\mathrm{mL}}}\right)^{2}$$

3

Here ℓ is estimated log post-cessation concentration, z is the one-sided standard-normal quantile, and $s^2 = \ln(1 + CV^2)$ converts a multiplicative coefficient of variation to log variance. Subscripts denote initial assay, volume, mapping and session calibration uncertainty. Independent reading error contributes the sum of squared normalized increments. The point integral required $\exp(\ell) \le$ the model target; integral-95 required $U \le$ that target. This first-order bound assumes the declared errors and is not a time-uniform confidence guarantee.

The two-level projection used measured concentrations at 60 and 180 minutes. With $A = \ln(C_1/C_2)$, $B = \ln[C_2(1 + r^*)/C_{target}]$, and active sampling interval Δ, the remaining time from the second sample was $R = \Delta B/A$. The nominal upper projection added zSE(R), with $Var(A) = 2\sigma^2$, $Var(B) = \sigma^2$ and $Cov(A,B) = -\sigma^2$ for independent equal-precision assays. Volume cancels from this time projection. The derivation is provided in Supporting Methods S1 (Supplementary file). This assay-only buffer cannot anticipate subsequent delivery changes.

Hybrid and fixed comparators

HYBRID-95 required both buffered criteria. Its eligible kinetic endpoint was the later component time:

$$T_{\mathrm{hybrid}} \;=\; \max\left(T_{\mathrm{integral\ 95}},\; T_{\mathrm{two-level\ 95}}\right)$$

4

An unavailable component rendered the hybrid unavailable; a component beyond the horizon prevented completion. The component errors were not assumed independent, so combining two nominal bounds did not establish a joint coverage probability. Under the model's monotonic decline, the later endpoint

cannot increase concentration relative to either completed component; the substantive comparison is the concentration–duration tradeoff.

The fixed-clearance frontier met every prespecified target: 16, 14, 12, 10, 8, 6, 5 mg/dL. All used measured initial concentration, estimated volume, the common post-cessation assumption, and 80% of nominal catalog clearance. The original Hirsch and Lachance prescriptions were also retained, including their published coefficients and concentration conversions, without added rebound adjustment or replacement half-lives.[3, 5] The lower-clearance use of Lachance remained an explicit extrapolation beyond its original setting.

To isolate treatment duration, three additional fixed timers retained the 16 mg/dL target and added a constant active-treatment interval. In separate calibration simulations, each constant was selected from 0–1800 minutes in 15-minute increments to minimize the median elapsed-time discrepancy from integral-95, two-level-95 or HYBRID-95. Ties selected the shorter extension. Calibration used observable kinetic times only, without concentration outcomes, and all candidates were retained. Each selected constant was then applied unchanged to the held-out evaluation sample. These scenario-specific benchmarks received knowledge of duration distributions, not patient-level latent truth.

Scenarios and endpoint handling

The original scenarios and all additions are listed in Table 1. In the primary model, underlying clearance had a mean of 280 mL/min and a standard deviation of 35, with serial correlation and transient reductions. True volume and mapping had a 10% CV; assay, calibration, and interval-reading CVs were 5%. Complete demographics, error laws, and operating assumptions are provided in Supporting Methods S1 (Supplementary file). These distributions are illustrative and not fitted to patient or device data.

Table 1
Prespecified scenarios and shared assumptions

ID	Scenario	Change from primary
0	Constant clearance	Clearance SD 0; dip probability 0
1	Variable clearance	Primary variable-clearance assumptions
2	Lower clearance	Mean 190; SD 30 mL/min; Lachance extrapolation
3	45-min interruption	Known pump-off from 180 to 225 min; all active clocks pause
4	Late clearance loss	Delivery multiplied by 0.65 after 240 min
5	Mapping 20% lower	True mapping ×0.8; assumed mapping unchanged
6	Volume 20% higher	True volume ×1.2; estimate unchanged
7	Post-stop increase 20%	True post-cessation fraction 0.2; assumed fraction 0.08
8	Greater declared noise	True and declared assay/reading CVs 10%
9	Biased correlated readings	Calibration ×1.1; reading log-error correlation 0.7; undeclared
10	Rebound fraction CV 10%	Fraction r has median 0.08, CV 10%; assumed fraction fixed
11	Rebound fraction CV 15%	Fraction r has median 0.08, CV 15%; assumed fraction fixed
12	Rebound fraction CV 25%	Fraction r has median 0.08, CV 25%; assumed fraction fixed
13	True noise 10%; declared 5%	True assay/reading CVs 10%; declared 5%
14	True noise 15%; declared 5%	True assay/reading CVs 15%; declared 5%
15	Mapping and volume bias	True mapping ×0.8 and volume ×1.2
16	Both biases plus late loss	Mapping ×0.8, volume ×1.2, plus late delivery ×0.65
17	True volume CV 20%	True volume CV 20%; declared 10%

a Each scenario has 5,000 evaluation and 5,000 separate timing-calibration sessions. Primary clearance: mean 280 mL/min, SD 35, AR(1) coefficient 0.85; 5% interval probability of a 50% dip. Declared CVs: volume and mapping 10%; assay, calibration and reading 5%.

b All error and post-cessation distributions are illustrative. Rebound CV applies to the fraction r, not the multiplier 1 + r. Unspecified assumptions remain those of the primary scenario; complete definitions and demographic distributions are in Supporting Methods S1.

New scenarios varied the nonnegative rebound fraction around a median of 8% using CVs of 10%, 15%, and 25%; the CV was applied to the fraction r, not to the full multiplier 1 + r. Other additions increased true assay and reading CVs to 10% or 15% while declared CVs remained 5%; combined mapping and

volume biases with and without later delivery loss; or increased true volume dispersion without changing its declared uncertainty.

All decisions were made on a 15-minute grid, with a 30-hour administrative horizon. Known pump-off intervals paused every active-treatment clock. Two-level criteria could not become eligible until the second result was available at 210 minutes. Nondeclining levels or either value ≤ 1.1 times the assumed 1 mg/dL quantification limit yielded no estimate. There was no shared dose cap, truth-informed rescue, or forced horizon endpoint.

Outcomes and statistical summaries

For each policy, we reported true post-cessation methanol ≥ 20 mg/dL, attainment of ≤ 16 mg/dL, concentration and elapsed-time distributions, and completion denominators. A separate composite counted threshold exceedance or no eligible endpoint within the horizon, using all sessions; it was a computational outcome, not a clinical adverse event. Positive paired time differences from the evaluator-only continuous 16 mg/dL crossing indicated longer modeled treatment, not proven unnecessary dialysis. Time quantiles treating unresolved endpoints as infinite were also provided.

Wilson intervals and Monte Carlo standard errors described the precision of the simulations. Paired risk contrasts used the standard error of within-session binary differences. Primary paired median-time contrasts used 2,000 bootstrap resamples; other scenarios reported paired medians and quartiles. Intervals were descriptive and conditional on calibration constants, without multiplicity adjustment or uncertainty from estimating those constants. Matching the median duration does not match the entire time distribution. Every fixed-grid point was retained; connecting lines did not imply tested intermediate prescriptions.

Random streams used NumPy's SeedSequence with master seed 20260914 and fixed integer scenario IDs. Calibration and random-rebound streams were identified separately. Code, configuration, calibration records, session outcomes, complete summaries, and document/figure-generation scripts are openly available on Zenodo (doi:10.5281/zenodo.22813727). Implementation tests and reproduction do not constitute independent human review or clinical validation.

Exploratory analyses

Exploratory additions were specified after the primary analysis and frozen before computation; they were not preregistered. We summarized mean durations and upper tails, paired hybrid-minus-fixed times, and model-reference times within timing strata. We varied result availability in the same primary sessions, distinguishing elapsed time from dialysis start from laboratory delay after the second sample at hour 3. We also generated 20,000 additional primary sessions using stream identifier 1000 and unchanged original calibration constants. Original analyses were retained without pooling or retuning.

Results

Primary risk and treatment duration

The evaluation comprised 90,000 sessions and 1,530,000 policy outcomes, with 90,000 additional timing-calibration sessions. In the primary scenario, all policies completed 5,000 evaluations except two-level-95 and HYBRID-95, each with 1 projected endpoint beyond the horizon (Table 2).

Table 2
Primary concentration and duration outcomes

Policy	≥ 20 mg/dL % (interval)	≤ 16 mg/dL %	Elapsed h median (IQR)	Excess min median (IQR)	Completed
Integral point	22.50 (21.36–23.68)	55.8	6.00 (4.75–7.50)	7 (-29–41)	5,000/5,000
Integral nominal 95%	0.60 (0.42–0.86)	97.6	8.00 (6.50–10.00)	117 (75–167)	5,000/5,000
Two-level point	7.80 (7.09–8.58)	66.5	6.00 (4.75–7.75)	11 (-7–33)	5,000/5,000
Two-level nominal 95%	1.00 (0.76–1.32)	91.6	6.50 (5.00–8.50)	38 (18–75)	4,999/5,000
HYBRID-95	0.02 (0.004–0.113)	99.7	8.25 (6.50–10.25)	127 (87–179)	4,999/5,000
Hirsch original	36.72 (35.39–38.07)	42.4	5.75 (4.50–7.00)	-12 (-54–27)	5,000/5,000
Lachance original	0.68 (0.49–0.95)	97.7	10.00 (8.25–11.25)	206 (144–272)	5,000/5,000
Fixed target 16	30.44 (29.18–31.73)	49.0	6.00 (4.75–7.25)	-1 (-43–37)	5,000/5,000
Fixed target 14	20.48 (19.38–21.62)	60.5	6.25 (5.00–7.50)	16 (-26–56)	5,000/5,000
Fixed target 12	13.72 (12.79–14.70)	72.7	6.50 (5.25–8.00)	36 (-4–77)	5,000/5,000
Fixed target 10	7.70 (6.99–8.47)	83.0	7.00 (5.75–8.50)	61 (19–104)	5,000/5,000
Fixed target 8	3.50 (3.03–4.05)	90.9	7.50 (6.25–9.00)	90 (48–135)	5,000/5,000
Fixed target 6	1.26 (0.99–1.61)	96.5	8.25 (6.75–9.75)	128 (83–176)	5,000/5,000
Fixed target 5	0.62 (0.44–0.88)	98.1	8.50 (7.25–10.25)	152 (106–203)	5,000/5,000
Fixed + 120 min	1.80 (1.47–2.21)	94.7	8.00 (6.75–9.25)	119 (77–157)	5,000/5,000
Fixed + 45 min	11.70 (10.84–12.62)	75.9	6.75 (5.50–8.00)	44 (2–82)	5,000/5,000
Fixed + 135 min	1.14 (0.88–1.47)	96.3	8.25 (7.00–9.50)	134 (92–172)	5,000/5,000

Policy	≥ 20 mg/dL % (interval)	≤ 16 mg/dL %	Elapsed h median (IQR)	Excess min median (IQR)	Completed
a Risk intervals are Wilson 95% intervals. Concentration and elapsed-time summaries use completed sessions. Two-level-95 and HYBRID-95 each have one horizon overrun; all other primary policies complete. Composite outcomes include noncompletion. Duration means and upper tails are in Supplementary file: Table S3; the additional 20,000-session analysis is reported separately in Supplementary file: Table S5.					
b Excess time is paired to the evaluator-only continuous 16 mg/dL crossing. Positive values do not establish unnecessary clinical treatment. IQR denotes interquartile range.					
c Fixed target-grid policies use the stated mg/dL target and the assumed post-cessation fraction. Fixed +minutes policies retain target 16 mg/dL and use an extension calibrated separately to integral-95, two-level-95 and HYBRID-95. Original Hirsch and Lachance prescriptions preserve their published parameters.					
Panel A shows the complete risk range; panel B enlarges the low-risk range. Solid squares are the prespecified fixed-clearance target grid, labeled in mg/dL. Filled symbols represent candidate policies; open symbols are fixed target-16 timers with 120, 45, 135 additional active minutes calibrated separately to integral-95, two-level-95 and HYBRID-95, respectively. Vertical intervals are Wilson intervals for Monte Carlo precision. Connected grid points do not represent tested intermediate targets. Concentration risks and median durations use completed sessions; two-level-95 and HYBRID-95 each have one horizon overrun. Complete denominators and the composite including noncompletion are in Table 2 and Supplementary file.					

Across the fixed target grid, ≥ 20 mg/dL exceedance declined from 30.44% to 0.62% as median duration increased from 6.00 to 8.50 hours. The integral point policy had 22.50% exceedance at 6.00 hours. Integral-95 had 0.60% at 8.00 hours, compared with 1.80% for its duration-calibrated fixed timer at the same median duration (Fig. 2).

Two-level-95 had 1.00% exceedance and median duration 6.50 hours. HYBRID-95 had 1/4,999 exceedances (0.02%; Wilson interval 0.004–0.113%) and 99.7% attainment of the model target, with median duration 8.25 hours. Its duration-calibrated fixed comparator had 57/5,000 exceedances (1.14%) at the same median duration. The fixed-grid target of 6 mg/dL also had that median duration and 1.26% exceedance; all other grid points were retained.

On 4,999 joint completers, HYBRID-95 minus its matched fixed comparator had a paired risk difference of -1.12 percentage points (Monte Carlo interval − 1.42 to -0.82). Counting noncompletion, the corresponding composite proportions were 0.04% and 1.14%. The median paired hybrid extension was 0 minutes over integral-95 and 75 minutes over two-level-95; these paired summaries differ from subtraction of group medians. Hybrid median excess over perfect-information target crossing was 127 minutes. Original Hirsch and Lachance results are retained in Table 2, without interpreting simulated performance as clinical invalidation of their published settings.

Among 4,999 primary joint completers, HYBRID-95 was shorter than its calibrated fixed timer in 48.9%, equal in 8.4% and longer in 42.7%. The paired median difference was 0 minutes, but the paired mean was

+ 9.5 minutes. In the shorter stratum (n = 2,445), median excess over the evaluator-only target crossing decreased from 152 minutes with the fixed timer to 99 minutes with the hybrid; in the longer stratum (n = 2,134), it increased from 102 to 171 minutes. All 57 fixed-timer exceedances occurred in the longer stratum, which had none under the hybrid. Conversely, the sole hybrid exceedance occurred in the shorter stratum, which had none under the fixed timer (Supplementary file: Table S3).

Primary completed-session p90/p95/maximum durations were 12.25/13.25/24.75 hours for the hybrid and 10.75/11.50/14.50 hours for its fixed comparator. The maximum paired hybrid extension was 795 minutes (Supplementary file: Table S3).

Misspecification and complementarity

With mapping 20% lower than assumed, integral-95 exceedance was 12.28%, compared with 1.64% for two-level-95 and 0.44% for HYBRID-95. After later clearance loss, the respective proportions were 0.40%, 25.80% and 0.26% (Fig. 3).

Combining mapping and volume biases increased integral-95 exceedance to 53.82% and hybrid exceedance to 1.61%. Adding later clearance loss produced the worst hybrid scenario: 1,229/4,946 exceedances (24.85%; interval 23.66–26.07%), with 54 additional horizon overruns. Its composite proportion was 25.66%. The hybrid's median duration was 11.25 hours, compared with 11.50 hours and 36.28% exceedance for the duration-calibrated fixed timer. Complementarity therefore reduced, but did not resolve, joint misspecification.

Under joint bias and later decline, completed-session p95 durations were 20.00 versus 14.75 hours, with maximum paired extension 1080 minutes. Treating unresolved endpoints as infinite raised hybrid p95 to 21.00 hours in that scenario; maxima among completers exclude those unresolved sessions (Supplementary file: Table S3).

Declared uncertainty and post-cessation variability

When true assay and reading CVs were 10% and 15% but declared CVs remained 5%, two-level-95 exceedance was 5.84% and 10.86%. Integral-95 yielded 0.68% and 0.80%; HYBRID-95 yielded 0.08% and 0.16%. In the more severe scenario, 2 hybrid estimates were unavailable and 42 exceeded the horizon, increasing its composite to 1.04%.

The random-rebound scenarios each produced 0.02% hybrid exceedance after rounding. These relatively small perturbations of the post-cessation multiplier did not establish a physiological rebound distribution or justify the assumed fraction. With increased true volume dispersion, integral-95 and hybrid exceedance were 4.22% and 0.18%. Complete results, calibration discrepancies, paired contrasts and all noncompletion counts are supplied in Supplementary file, with the complete machine-readable data available in Zenodo (doi:10.5281/zenodo.22813727).

Exploratory sensitivity analyses

When results became available at hour 8 from dialysis start (a 5-hour delay after sampling), hybrid median duration remained 8.25 hours, but 45.4% of session times changed and mean duration rose from 8.46 to 9.32 hours. Exceedances fell from 1 to 0 among 4,999 completers. Availability at hours 10 and 12 raised medians to 10.00 and 12.00 hours. An 8-hour laboratory delay instead meant availability at hour 11 and median duration 11.00 hours. One horizon overrun persisted throughout. These results quantify modeled waiting burden, not clinical benefit or futility (Supplementary file: Table S4).

All 20,000 additional hybrid sessions completed, with 2 exceedances (0.010%; Wilson interval 0.003–0.036%). Its calibrated fixed timer had 264 exceedances (1.32%); both medians were 8.25 hours. The paired risk difference was − 1.31 percentage points (interval − 1.47 to -1.15). Paired mean extension remained + 9.5 minutes. The fixed-6 grid timer had median 8.00 hours, so its duration did not exactly match the hybrid in this sample. The additional synthetic sessions do not provide external validation (Supplementary file: Table S5).

Discussion

The expanded comparison supports complementary use of delivered-clearance observations and timed methanol measurements within the specified model. Their combination improved concentration outcomes at comparable median duration in the primary scenario and several misspecification scenarios. Conservative fixed timers also substantially lowered exceedance as treatment lengthened. Reporting that frontier and using separate duration calibration distinguishes some information benefit from the general effect of longer dialysis.

The hybrid result requires careful interpretation. Requiring a later endpoint necessarily lowers concentration in this monotonic model; that property alone is not evidence of useful clinical prediction. The paired results show shorter and longer individual courses with a greater mean and upper tail, despite matched medians. Thus lower exceedance was not achieved without additional treatment burden. The hybrid can also inherit an unavailable or extremely late two-level projection. Completed-session risk must be read alongside noncompletion, tail durations and the composite outcome.

The two measurements answer different questions. The integral tracks reported delivery throughout treatment but depends on estimated volume and the dialysance-to-methanol mapping. The two-level projection estimates the observed concentration decline directly, avoiding those assumptions in the time calculation, but depends on the sampled interval representing subsequent treatment. These are complementary sources of information, not statistically independent signals. Combined mapping-volume errors and later clearance loss can compromise both, as the joint scenario demonstrated.

Methanol is a small, water-soluble solute with low protein binding and is efficiently dialyzable.[1] Ionic dialysance is therefore a mechanistically plausible small-solute surrogate, but its quantitative mapping to systemic methanol clearance remains empirically uncalibrated for this application. Lower molecular weight alone does not establish a mapping factor at or above unity. Access recirculation, sampling

location, the device's conductivity method and distinctions between dialyzer and systemic clearance can affect interpretation.[6, 7] Intercompartmental transfer, if relevant, would require a different kinetic model rather than an unsupported correction factor. Repeated readings cannot remove a persistent calibration bias.

Watson is an established anthropometric estimator, not a defective formula.[10] Its performance as a methanol distribution-volume estimate in severe poisoning, acidosis, fluid resuscitation, obesity or other physiological disturbance remains uncertain. Stable-isotope studies in acute renal failure demonstrate that urea distribution space and body-water estimates need not coincide, but those observations do not supply a methanol-specific error distribution.[12] The simulation's sensitivity to volume underestimation therefore identifies a calibration need; it does not estimate the frequency or magnitude of that error in poisoned patients.

The post-cessation model is another substantive limitation. A multiplicative increase was imposed on the concentration endpoint rather than generated by redistribution or absorption. Published reports of re-elevation do not establish a universal rebound fraction.[11] Varying the fraction across sessions tests one form of uncertainty while leaving the kinetic mechanism unspecified. Likewise, the true and declared assay and reading errors were deliberately separated, but the selected CVs do not characterize a particular laboratory or dialysis console.

All findings are conditional on the chosen population, clearance process, error distributions and one-compartment assumptions. The simulations omit changing volume, continued absorption, endogenous elimination, incomplete antidote blockade, formate kinetics and clinical recovery. The first-order nominal bounds lack guaranteed coverage under repeated assessment. Monte Carlo intervals quantify numerical precision rather than these structural uncertainties; the duration-comparator intervals additionally condition on estimated calibration constants. Complete scenario reporting limits selective presentation but cannot establish robustness to every plausible clinical course.

Clinical cessation must remain a separate decision. Methanol concentration may cease to be the binding criterion when acidosis, formate-related toxicity or an evolving clinical course persists.[1, 2] The calculator is consequently labeled a research prototype and reports modeled kinetic criteria, with no instruction to stop dialysis. It cannot supply a future integral-based time without subsequent observed delivery. A combined historical reassessment time is displayed only when the available concentration results and complete observed delivery establish both criteria.

A next empirical study should pair device-specific dialysance with appropriately sampled systemic methanol concentrations, characterize assay and volume uncertainty, and examine changes in delivery after sampling. Evaluation should include calibration of predicted concentrations, delayed or unavailable results, post-treatment concentrations, biochemical recovery and clinicians' reasons for continuing treatment after a kinetic criterion is met. Such work would determine whether the simulated information

benefit is clinically useful and whether combining measurements justifies its treatment and measurement burden.

Conclusions

Delivered-clearance integration and timed concentration projection had complementary strengths in simulation. Their conjunction improved the concentration–duration tradeoff in several settings, but simultaneous errors defeated both components. These findings support empirical calibration and further evaluation of a research framework; they do not validate a clinical dialysis cessation rule.

Abbreviations

AR(1)
first-order autoregressive process
CV
coefficient of variation
EXTRIP
Extracorporeal Treatments in Poisoning
IQR
interquartile range
MCSE
Monte Carlo standard error
SD
standard deviation
SE
standard error.

Declarations

Ethics approval and consent to participate

Not applicable. No new human-participant or animal data were collected. The study used synthetic data and a limited arithmetic illustration based on previously published estimates.

AI-assisted manuscript preparation:

ChatGPT (OpenAI) was used solely for language editing and manuscript formatting. The author reviewed and approved all AI-assisted revisions and takes full responsibility for the final content.

Clinical trial number: not applicable.

Consent for publication:

Not applicable.

Availability of data and materials

All study data are synthetic. The complete simulation data, calibration records, frozen analysis plans, source code, tests, machine-readable outputs, data dictionaries, verification records, document/figure-generation scripts, and reproducibility materials are openly available on Zenodo at https://zenodo.org/records/22813727. Supporting Methods S1 and condensed Tables S1–S5 are provided as Supplementary file. The published-case arithmetic illustration uses previously reported estimates and does not constitute external validation.

Competing interests

The author declares no competing interests.

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Authors' contributions

OM conceptualized the study, developed the methodology and software, performed the simulations and formal analyses, generated the visualizations, and wrote and revised the manuscript. The author read and approved the final manuscript.

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Figures

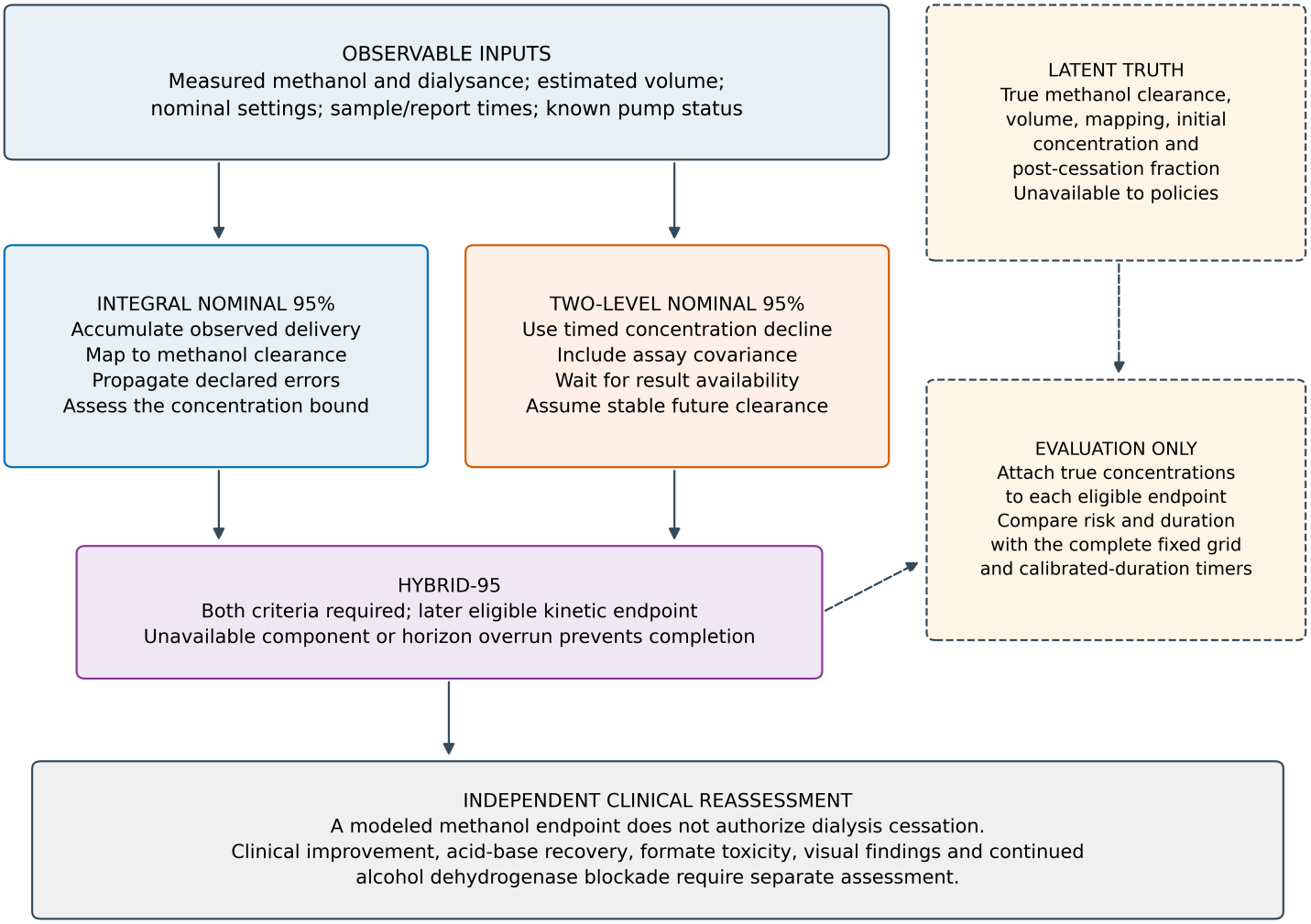
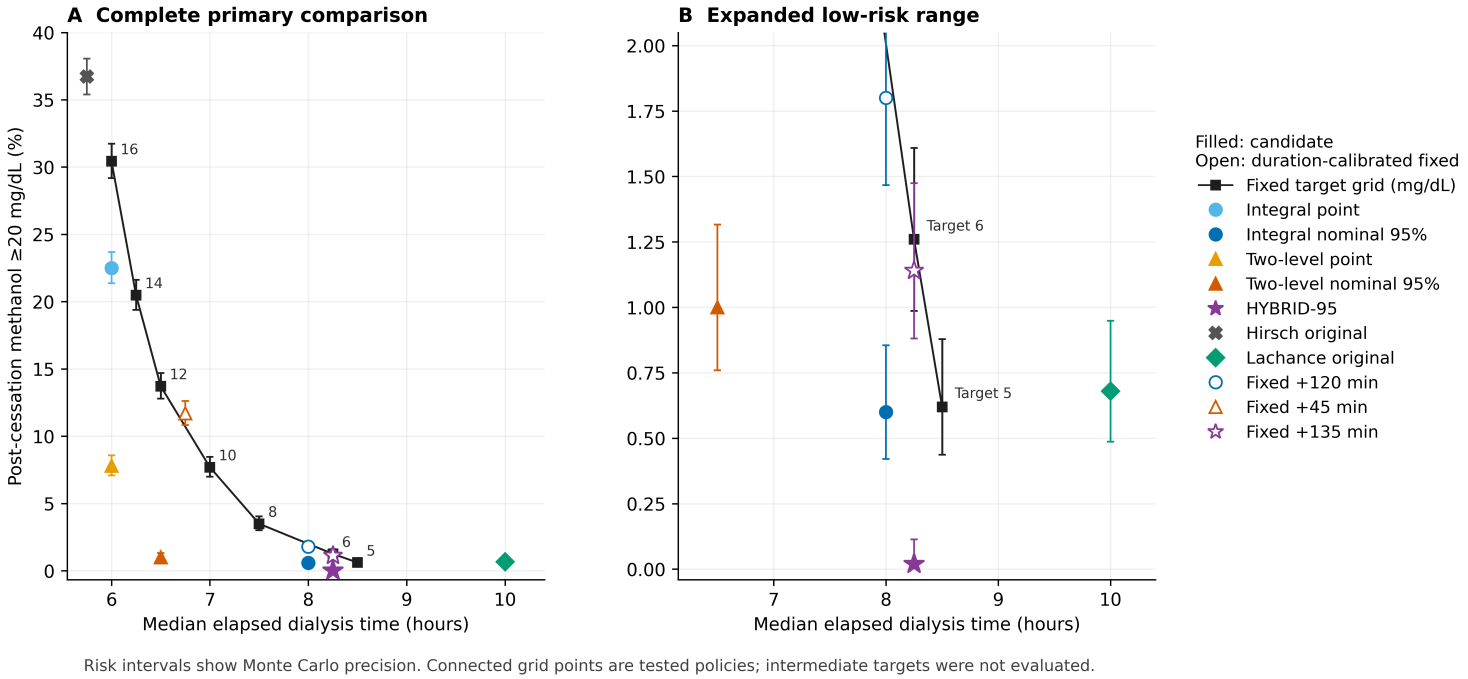


Figure 1

Information flow in the research framework.

Policies receive observable inputs only. Latent truth is reserved for evaluating true concentration outcomes and the perfect information reference. The hybrid requires both nominal criteria; unavailable components and horizon overruns remain explicit. A kinetic endpoint is distinct from the clinical assessment needed to consider dialysis cessation.

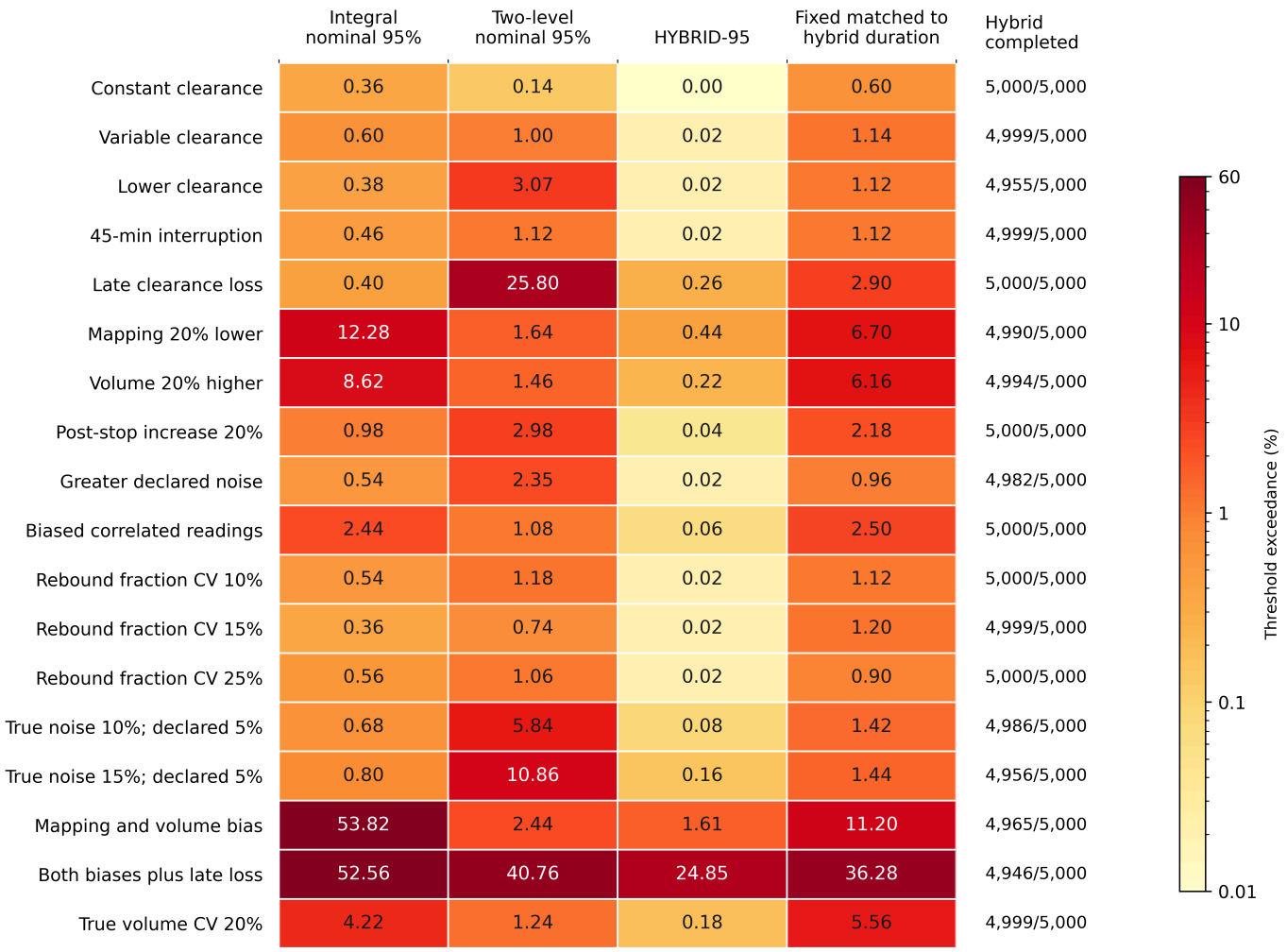


Risk intervals show Monte Carlo precision. Connected grid points are tested policies; intermediate targets were not evaluated.

Figure 2

Primary risk–duration comparison in 5,000 held-out sessions per policy.

Panel A shows the complete risk range; panel B enlarges the low-risk range. Solid squares are the prespecified fixed-clearance target grid, labeled in mg/dL. Filled symbols represent candidate policies; open symbols are fixed target-16 timers with 120, 45, 135 additional active minutes calibrated separately to integral-95, two-level-95 and HYBRID-95, respectively. Vertical intervals are Wilson intervals for Monte Carlo precision. Connected grid points do not represent tested intermediate targets. Concentration risks and median durations use completed sessions; two-level-95 and HYBRID-95 each have one horizon overrun. Complete denominators and the composite including noncompletion are in Table 2 and Supplementary file.



Percentages use completed-session denominators. Zero events are shown as 0.00, not as proof of zero risk.
The composite including noncompletion and full uncertainty intervals are reported in the supporting tables.

Figure 3

True post-cessation methanol ≥20 mg/dL across all 18 prespecified scenarios. Cells show percentages among completed sessions. The rightmost policy is the fixed target-16 timer with a scenario-specific constant extension calibrated to hybrid median duration using separate sessions. Hybrid completion denominators are printed beside the matrix. Color uses a logarithmic scale; zero events are displayed at the lowest color and labeled 0.00, without implying zero risk. All Wilson intervals, duration discrepancies and composite outcomes including noncompletion are supplied in Supplementary file and the Zenodo repository (doi:10.5281/zenodo.22813727).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary.docx