

# In silico ordinary differential equation/partial differential equation hemodialysis model estimates methadone removal during dialysis

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**Background:** There is a need to have a model to study methadone's losses during hemodialysis to provide informed methadone dose recommendations for the practitioner.

**Aim:** To build a one-dimensional (1-D), hollow-fiber geometry, ordinary differential equation (ODE) and partial differential equation (PDE) countercurrent hemodialyzer model (ODE/PDE model).

**Methodology:** We conducted a cross-sectional study in silico that evaluated eleven hemodialysis patients. Patients received a ceiling dose of methadone hydrochloride 30 mg/day. Outcome measures included: the total amount of methadone removed during dialysis; methadone's overall intradialytic mass transfer rate coefficient,  $k_m$ ; and, methadone's removal rate,  $j_{ME}$ . Each metric was measured at dialysate flow rates of 250 mL/min and 800 mL/min.

**Results:** The ODE/PDE model revealed a significant increase in the change of methadone's mass transfer with increased dialysate flow rate,  $\% \Delta k_m = 18.56$ ,  $P=0.02$ ,  $N=11$ . The total amount of methadone mass transferred across the dialyzer membrane with high dialysate flow rate significantly increased ( $0.042 \pm 0.016$  versus  $0.052 \pm 0.019$  mg/kg,  $P=0.02$ ,  $N=11$ ). This was accompanied by a small significant increase in methadone's mass transfer rate ( $0.113 \pm 0.002$  versus  $0.014 \pm 0.002$  mg/kg/h,  $P=0.02$ ,  $N=11$ ). The ODE/PDE model accurately predicted methadone's removal during dialysis. The absolute value of the prediction errors for methadone's extraction and throughput were less than 2%.

**Conclusion:** ODE/PDE modeling of methadone's hemodialysis is a new approach to study methadone's removal, in particular, and opioid removal, in general, in patients with end-stage renal disease on hemodialysis. ODE/PDE modeling accurately quantified the fundamental phenomena of methadone's mass transfer during hemodialysis. This methodology may lead to development of optimally designed intradialytic opioid treatment protocols, and allow dynamic monitoring of outflow plasma opioid concentrations for model predictive control during dialysis in humans.

**Keywords:** methadone, hemodialysis, renal failure, modeling

## Introduction

Methadone is a synthetic full opioid receptor mu-1 (OPRM1) agonist for oral dosing with affinity for the NMDA receptor.<sup>1</sup> It is a Drug Enforcement Agency Schedule II controlled substance metabolized mostly by the Phase I hepatic CYP 3A4 system, and to a lesser extent, by *CYP2D6*, *CYP2C8*, *CYP2C19*, *CYP2B6*, and *CYP1A2* to seven metabolites including two minor active metabolites: methadol and normethadol.<sup>2,3</sup> Methadone consists of two enantiomers, the d- and l-isomers, the former is responsible for analgesic activity. The l-isomer is dependent on 2B6 metabolism. Foreseeable accumulation of the l-isomer by poor 2B6 metabolizers consequently elevates

risk for cardiotoxicity.<sup>4,5</sup> Methadone and its metabolites are almost equally excreted in urine and feces.<sup>6</sup> Notwithstanding, however, there is a 30-fold variability in the liver *CYP3A4* and 11-fold in the intestinal *CYP3A4* enzymes.<sup>7,8</sup> But, in patients with anuria, methadone is metabolized by the gastrointestinal system<sup>9</sup> and excreted only in the feces.<sup>10</sup>

Hemodialysis involves passing a patient's blood through an extracorporeal circuit with a synthetic membrane attached. Plasma water and small molecular weight (MW) <500 Da solutes, including methadone hydrochloride (MW 345.91 Da), are readily removed from the blood by convective and diffusive forces and are lost as ultrafiltrate.<sup>11</sup> However, hemodialysis causes little change in pre-dialysis compared with post-dialysis plasma methadone concentrations,<sup>12</sup> which means that hemodialysis removes only a small portion of methadone from blood. This intuitively makes methadone an attractive opioid for the management of chronic pain in patients undergoing dialysis.<sup>13</sup>

Nonetheless, any methadone removed during dialysis may be important and require adjusting or supplementing a patient's routine dose regimen when dosed three to four times daily for analgesia. Supplementing a patient's methadone dose regimen would be particularly relevant for a hemodialysis patient undergoing treatment for substance abuse or pain management with methadone. Supplementation may be needed to prevent methadone levels from falling below their minimum effective concentrations,<sup>14</sup> which could precipitate acute withdrawal, pain crisis, or both. No recommendations

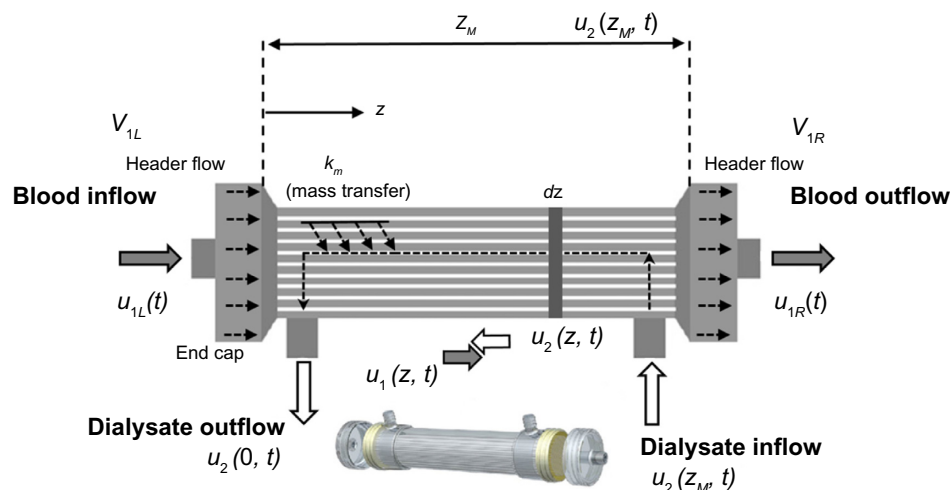
currently exist for methadone's use in patients undergoing hemodialysis. No information is available to guide dosing. Therefore, there is a need to have a model to study methadone's losses during hemodialysis to provide informed methadone dose recommendations for the practitioner.

We built a one-dimensional (1-D), hollow-fiber geometry, ordinary differential equation (ODE) and partial differential equation (PDE) countercurrent hemodialyzer model (ODE/PDE model). The ODE/PDE model mimicked methadone's disposition during hemodialysis. We used this ODE/PDE model to measure methadone's intradialytic mass transfer and removal rate. To determine whether the model could detect an expected increase in methadone's removal with increased dialysate flow, we measured methadone's removal at dialysate flow rates of 250 mL/min and 800 mL/min. The ODE/PDE model allowed us to implement a clinical strategy for estimating a patient's post-hemodialysis methadone restoration dose.

## Methods

### Subjects and protocol

To develop the model, we used the data from the published experiments by Perlman et al.<sup>12</sup> The data were digitally extracted from their publication using high-resolution image processing with GIMP version 2.8 (<http://www.gimp.org/>), and measured using UN-SCAN-IT version 6.0 software (Silk Scientific, Orem, UT, USA). A similar approach has been successfully used to study the dynamic



**Figure 1** ODE/PDE model of one-dimensional (1-D) counter current hemodialyzer with distance  $z$  of the spatial boundary independent variable along the dialyzer.

**Notes:** Time  $t$  is the temporal initial value independent variable. The two PDE dependent variables,  $u_1(z, t)$  and  $u_2(z, t)$ , represent normalized methadone concentrations in the blood and dialysate, respectively.  $Z_M$  stands for the length of the dialyzer membrane excluding the headers. In this model, blood enters the left end of the dialyzer at a normalized methadone blood concentration of  $u_{1L}(t)$ .  $V_{1L}$  is the header flow volume at the left end. The exiting normalized methadone blood concentration at the right end is  $u_{1R}(t)$ .  $V_{1R}$  is the header flow volume at the right end. The entering and exiting dialysate concentrations are  $u_2(z = z_M, t)$  and  $u_2(z = 0, t)$ . The header is the space enclosed by the end cap of the dialyzer and the polyurethane potting material that holds the hollow fibers together (inset).

**Abbreviations:** ODE, ordinary differential equation; PDE, partial differential equation.

relationship between glucose, insulin and non-esterified fatty acids.<sup>15,16</sup>

We studied eleven patients (see Table 1). Patients received a ceiling dose of methadone hydrochloride (hereafter methadone) in divided doses totaling 30 mg/day for patients receiving other than once daily dosing for analgesic purposes. Specific details including dose escalation of opioid-naïve patients to reach the ceiling dose are provided by Perlman et al.<sup>12</sup> This research was conducted according to ethical principles in the World Medical Association Declaration of Helsinki (59th WMA General Assembly, Seoul, October 2008), which includes research on published human data. The study was approved by the Emerio & Lourdes Linares Research and Education Center Institutional Review Board.

## Dialyzer model development

Hemodialysis experiments to test the model were performed in silico. On the one hand, we compared methadone's mass transfer to that of a perfect reference standard. On the other hand, we compared methadone's mass transfer at dialysate flow rates we defined as low, equal to 250 mL/min, and high, equal to 800 mL/min. For each patient, hemodialysis blood flow rates were held constant at 250 mL/min. We sought to identify a potential dependence of methadone's removal on dialysate flow rate. If the model could detect such a dependence, it would serve as a test of the model's sensitivity to detect a mechanism-based change.

We implemented the ODE/PDE model illustrated in Figure 1. Dialyzer geometry refers to the cross-sectional area in contact with the blood, semipermeable membrane, and dialysate. Table 2 presents a glossary of symbols and units.

Closely following Schiesser,<sup>17</sup> as shown in Figure 1, the ODE/PDE model is 1-D with distance  $z$  the spatial boundary

**Table 1** Patient demographics

Patient	Age (years)	BMI	Sex	Cause of pain
1	70	20.2	F	Colon cancer
2	66	21.1	M	Chronic low back pain
3	84	19.5	F	Osteoarthritis
4	81	24.6	M	Chronic low back pain
5	84	25.3	M	Chronic low back pain
6	60	32.6	M	Peripheral vascular disease
7	70	29	M	Polyneuropathy
8	81	24.6	M	Chronic low back pain
9	41	46.8	F	SLE myopathy/neuropathy
10	71	26.6	F	Rhabdomyosarcoma
11	84	25.3	M	Chronic low back pain

**Abbreviations:** BMI, body mass index; F, female; M, male; SLE, systemic lupus erythematosus.

**Table 2** Glossary of symbols and units

Symbolism	Interpretation	Units <sup>a</sup>
$u_1$	Plasma methadone concentrations	ng/mL
$u_2$	Dialysate methadone concentrations	ng/mL
$E$	Extraction	%
$T$	Throughput	%
$V_{IL}, V_{IR}$	Left and right header flow volumes	cm <sup>3</sup>
$t$	Time	min
$z$	Axial spatial position along dialyzer	cm
$Z_M$	Dialyzer membrane length excluding headers	cm
$A$	Dialyzer cross-sectional area (transverse to $z$ )	cm <sup>2</sup>
$\xi$	Blood flow fraction of $A$	—
$v_1, v_2$	Blood and dialysate linear flow velocities, respectively	cm <sup>3</sup> /min
$A_M$	Area for mass transfer per unit length in $z$	cm <sup>2</sup> /cm
$k_m$	Mass transfer coefficient	cm/s
$D$	Dialyzer diameter	cm
$D$	Methadone's diffusivity	cm <sup>2</sup> /s
$j_{ME}$	Methadone's intradialytic removal rate	mg/kg/h
$q_1, q_2$	Blood and dialysate volumetric flow rates, respectively	cm <sup>3</sup> /min
$u_{IL}$	Normalized inflow blood methadone concentration	Dimensionless
$u_{IR}$	Normalized outflow blood methadone concentration	Dimensionless
$V_{IL}, V_{IR}$	Header volumes	cm
$Z_M$	Dialyzer length excluding headers	cm
$\xi$	Fraction of $A$ available for blood flow ( $0 \leq \xi \leq 1$ )	Dimensionless
$V_{IL}$	Volume on the left	cm <sup>3</sup>
$V_{IR}$	Volume on the right	cm <sup>3</sup>

**Notes:** <sup>a</sup>units: 1 mcg = 1,000 ng and 1 L = 1,000 mL; converting mL to L gives 1 mcg/L/1 L = 1,000 ng/1,000 mL, so that 1 mcg/L = 1 ng/mL; 1 mm = 0.1 cm; 1 h = 3,600 s; 1 mcg = 0.001 mg.

**Abbreviations:** h, hours; s, seconds; min, minutes.

independent variable along the dialyzer. Time  $t$  is the temporal initial value independent variable. The two PDE dependent variables,  $u_1(z, t)$  and  $u_2(z, t)$ , represent normalized methadone concentrations in the blood and dialysate, respectively, and  $z$  stands for the length of the dialyzer excluding the headers. The independent time variable is  $t$  in minutes. The derivation of the ODE/PDE model equations are presented in the Supplementary material.

Figure 1 also shows blood enters the left end of the dialyzer at a methadone blood concentration of  $u_{1L}(t)$ . This boundary condition is not defined as  $u_1(z = 0, t)$  due to the header flow volume at the left end,  $V_{IL}$ . Similarly, the exiting methadone blood concentration at the right end is  $u_{1R}(t)$  rather than  $u_1(z = z_M, t)$  because of the header flow volume there also,  $V_{IR}$ .  $Z_M$  stands for the length of the dialyzer membrane excluding the headers. The entering and exiting dialysate concentrations are  $u_2(z = z_M, t)$  and  $u_2(z = 0, t)$ .

The header is the space enclosed by the end cap of the dialyzer and the polyurethane potting material that holds the hollow fibers together (inset Figure 1). The header forms a barrier between the blood and dialysate compartments. Headers channel blood from the dialyzer inlet into the membrane fibers, and from the membrane fibers into the dialyzer outlet. The end caps can be removed from some dialyzers (inset Figure 1). The headers can be assumed to be well mixed and therefore modeled with ODEs. The dialyzer membrane passage is distributed in space and time so we use PDEs. Thus, ODE/PDE model results which are easily handled with the method of lines (MOL).<sup>18</sup> Note, the headers serve as low-pass filters in the sense that they smooth abrupt changes such as step changes at the inlet.

Our objective in formulating our experiments with the model and computing numerical solutions with it was to determine  $u_1(z, t)$  and  $u_2(z, t)$ , and in particular, how methadone's mass transfer reduced the outflow methadone concentration,  $u_{1R}(t)$ , below its inflow value,  $u_{1L}(t)$ . This approach allowed us to perform a methadone mass balance on the blood and thereby estimate methadone's mass transfer coefficient,  $k_m$  (see Supplementary material).

Our objective was not to examine the efficiency of a particular commercially available dialyzer to remove methadone from blood. Therefore, we set the ODE/PDE model parameters to arbitrary, though realistic values, comparable to those of commercially available dialyzers<sup>19,20</sup> as follows: D: dialyzer diameter 5 cm; A: dialyzer cross-sectional area equal to  $\pi \times D^2 \text{ cm}^2$  (used in Equations S1 and S2 [see Supplementary materials]);  $A_M$ : dialyzer mass transfer area per unit length of dialyzer  $\text{cm}^2/\text{cm}$  (used in Equations S2 and S3). We set  $A_M = A$ ;  $q_1, q_2$ : volumetric flow rate of blood equal to  $0.25 \times 10^3$  and dialysate equal to  $0.25 \times 10^3 \text{ cm}^3/\text{min}$ , respectively;  $\xi$ : fraction of A available for blood flow,  $0 \leq \xi \leq 1$ , dimensionless. Hence,  $1 - \xi$  is the fraction of A available for dialysate flow;  $v_1, v_2$ : linear flow velocities for blood, equal to  $q_1/\xi \times A$ , and dialysate, equal to  $-q_2/[(1 - \xi) \times A]$ , respectively,  $\text{cm}^3/\text{min}$  (used in Equations S2 and S3). Note, for countercurrent flow,  $v_1 > 0$  and  $v_2 < 0$ , which maximizes methadone's convective and diffusive mass transfer;  $u_{1L}$ : normalized inflow blood methadone concentration equals 1, as  $z=0$ , dimensionless;  $V_{1L}, V_{2R}$ : header volumes for  $u_1$  at  $z=0$ ,  $z_M$ , are  $\text{cm}^3$ . The length of these header volumes is 1 cm ( $v_{1L} = 1 \times A$ ). However, these values cannot be zero because of the division by the volume in the numerical integration of the ODEs in Equations S5 and S6;  $u_{10}, u_{20}$ : initial

conditions (ICs) for Equations S2 and S5 equal zero, respectively, and dimensionless (in Equation S4:  $u_1(z, t = 0) = f_1(z) = u_{10}$  and  $u_2(z, t = 0) = f_2(z) = u_{20}$ , respectively);  $Z_M$ : dialyzer length equal to 50 cm;  $n$ : number of grid points in  $z$  equal to 51.

Methadone's mass transfer coefficient from blood into dialysate,  $k_m$ , was estimated by solving the coefficients in Equations S1 and S2. Detailed MATLAB (matrix laboratory) code for estimating methadone's  $k_m$  using the MOL to solve the ODE/PDE model is provided in Schiesser's work.<sup>17</sup>

## Hemodialysis experiments

In brief, Perlman et al<sup>12</sup> improved methadone pain control in their patients over a 2-week period. After this 2-week period, blood samples were drawn during the patients' first scheduled dialysis session. The first sample was drawn immediately before starting dialysis and the last sample was drawn immediately after the 4-hour dialysis session. Patients were instructed to take their last dose of methadone 6 hours before starting dialysis to make sure that plasma methadone concentrations were measured during the elimination phase. This may be a limitation for maintenance therapy patients as they receive their dose early in the day. However, this schedule enables accurate assessment of methadone's elimination with minimal influence from absorption or redistribution.<sup>21</sup> Patients did not receive extra or breakthrough doses of methadone during dialysis. Acetaminophen was used to treat pain during dialysis.

Perlman et al<sup>12</sup> measured methadone serum concentrations using liquid chromatography tandem mass spectrometry.<sup>22</sup> In non-dialysis patients, plasma methadone levels increased linearly by 260 ng/mL for every 1 mg/kg of methadone ingested.<sup>23</sup> The coefficient of variation and accuracy for all standards were within the acceptable range of 20% of the lower limit of detection and 15% of other standards and quality control samples. Linearity was achieved in the analytical ranges of 0.5 to 300 ng/mL. For all calculations and ODE/PDE modeling, the published methadone concentration for an individual time point for the first and second dialysis sessions were combined and averaged. Methadone's intradialytic extraction ratio was calculated from the simultaneously sampled arterial (inflow) and venous (outflow) plasma methadone concentrations by dividing their difference by the arterial plasma methadone concentration (see results, Table 3). Full details of the experimental protocol and procedures utilized by Perlman et al have been previously described in detail.<sup>12</sup>

**Table 3** Experimentally measured plasma methadone concentrations versus ODE/PDE model predictions<sup>a,b</sup>

	Measured N=11	Model N=11	Error (%)
Inflow	46.14±14.07	46.13±14.07	0.36±0.15
Outflow	36.36±10.79	36.33±10.78	1.85±4.43
E	19.84±3.01	20.52±2.92	0.61±0.49
T	80.16±3.01	79.58±2.89	0.68±0.60

**Notes:** <sup>a</sup>Values are mean ± SE; inflow and outflow are ng/mL (equal to µg/L); E is extraction and T is throughput in percent. <sup>b</sup>Measured versus model all  $P>0.05$  by dependent 2-group Wilcoxon signed rank test.

**Abbreviations:** ODE, ordinary differential equation; PDE, partial differential equation; SE, standard error.

## Statistics

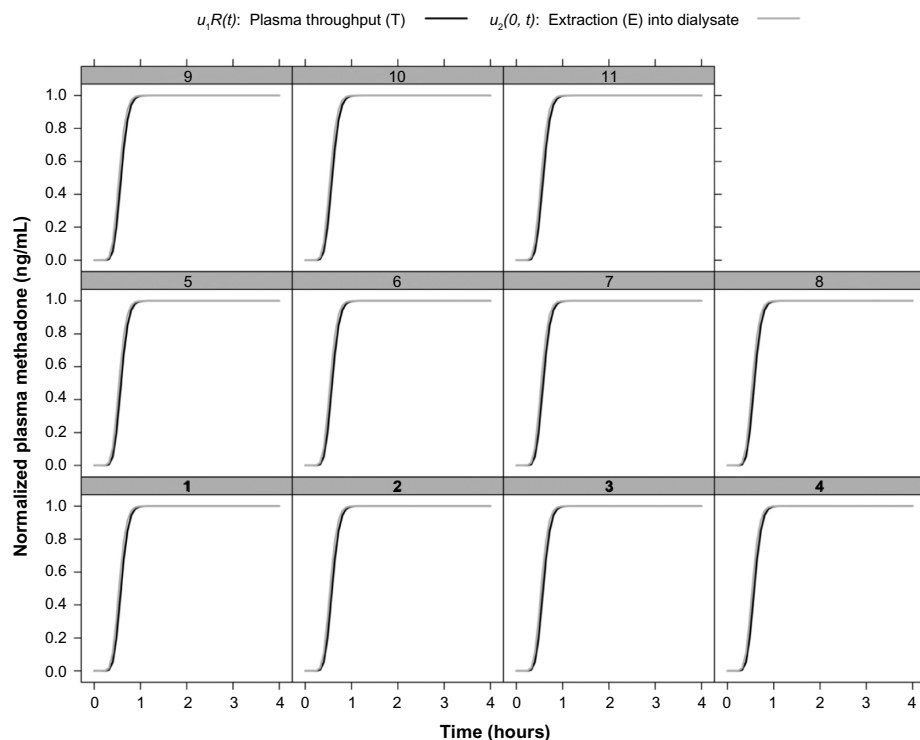
Statistical analyses were performed using R version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Solution of the ODE/PDE model was performed using MATLAB MOL codes<sup>20</sup> translated into R.<sup>24,25</sup> A sample size of eleven was calculated to be the smallest  $n$  that would achieve a power of 90% to detect a 2% difference with  $\alpha=5\%$  between the measured and ODE/PDE model predicted values.<sup>26</sup> All values are mean ± standard deviation unless otherwise indicated. Values in brackets are 95% confidence intervals (95% CIs). Mathematical computations with error propagation were performed using Mathematica 10.1 (Wolfram Research, Champaign, IL, USA). A significant

difference or relationship was established when the probability of rejecting the null hypothesis was  $\leq 0.05$ .

## Results

For each patient, Figure 2 shows the plots for the case where no methadone mass transfer into the dialysate occurred, ie,  $k_m=0$ . This simulation is used for reference. The two solutions,  $u_{1R}(t)$  and  $u_2(z=0, t)$ , are close. Both have the same inflow values:  $u_{1L}=u_{2zM}=1$ . However, the solutions are not exactly the same because of the blood flow at the inflow and outflow headers (Figure 1). As expected, the responses of the normalized plasma methadone concentrations with headers (black curves),  $u_1(z, t)$ , are slightly delayed compared to those for the dialyzer with no headers (gray curves). Both solutions approach 1 with increasing  $t$  as expected because when there is no mass transfer ( $k_m=0$ ), the entire unit inflow plasma methadone concentrations move through the system and exit.

Both solutions in Figure 2,  $u_{1R}(t)$  and  $u_2(z=0, t)$ , reflect a traveling wave<sup>27</sup> that results from the PDE's ICs  $u_{10}=u_{20}=0$ . The inflow unit methadone concentrations travel through the dialyzer and eventually reach the outflow, at which time both solutions move from the zero ICs to the unit boundary conditions. The step is not instantaneous because of the so-called numerical diffusion (which is not physically

**Figure 2** One-dimensional (1-D) ODE/PDE model's perfect reference standard response with zero mass transfer of methadone into dialysate.

**Abbreviations:** ODE, ordinary differential equation; PDE, partial differential equation.



realistic) from the two point upwinding of the derivatives in  $z$  of Equations S2 and S3. However, we largely eliminated numerical diffusion by using flux limiters.

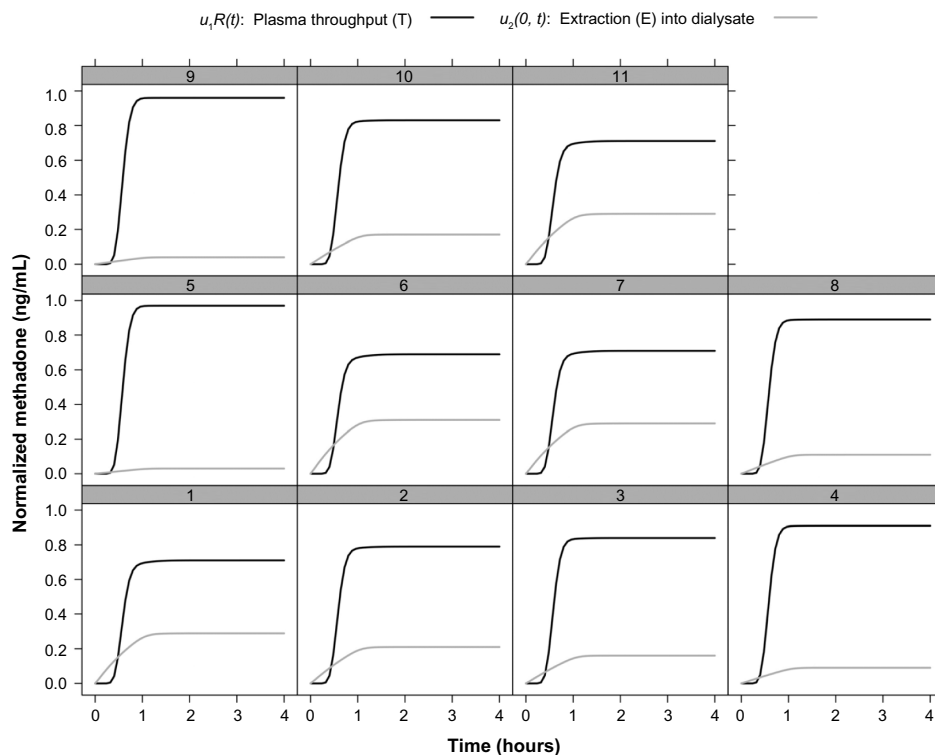
The arrival time of methadone molecules at the outflow (right end,  $z = z_M$ ) for  $u_1$  can be estimated as  $z_M/v_1 = 50 \text{ cm} \div 0.025 \text{ cm/s} = 2,000 \text{ s} = 0.56 \text{ hour}$ . Similarly, for  $u_2$ , since  $v_2 = -v_1$  the arrival time at the left end ( $z=0$ ) is also approximately 0.56 h. These arrival times may not be exact due to some numerical diffusion and the delay in methadone's  $u_1$  response due to the two headers. Notice, while the time for convection through the dialyzer may be of the order of minutes, the time to reach equilibrium or steady state can be considerably longer because of the interaction of the blood and dialysate streams through the membrane mass transport.

Table 3 presents results of the experimentally measured versus the ODE/PDE model predicted plasma methadone inflow and outflow concentrations, and their extraction (E) and throughput (T), by and through the dialyzer, respectively. Table 3 shows that the ODE/PDE model accurately predicted methadone's experimentally measured values. There were no significant differences between methadone's experimentally measured values and the ODE/PDE model predictions (all  $P > 0.05$ ). In addition, the absolute value of the prediction

errors for methadone's intradialytic E and T were less than 2%.

Figure 3 shows the case where each patient's methadone  $k_m$  was estimated with the ODE/PDE model using the measured experimental data presented in Table 3. Blood and dialysate flow rates were set equal to 250 mL/min. Methadone's  $k_m$  was equal to  $3.64 \times 10^{-3} \pm 2.16 \times 10^{-5} \text{ cm/min}$ . Compared to the solutions in Figure 2, the two solutions in Figure 3,  $u_{1R}(t)$  and  $u_2(z=0, t)$ , are not so close. Although both solutions have the same normalized inflow values:  $u_{1L} = u_{2z_M} = 1$ , their normalized outflow values were significantly different. At  $t = 4 \text{ h}$ ,  $u_{1R}(t) = 0.824 \pm 0.013$  with a 95% CI (0.723, 0.922), and  $u_2(z=0, t) = 0.175 \pm 0.013$  with a 95% CI (0.076, 0.274),  $P < 0.05$ . Methadone's maximum extraction during dialysis occurred at  $1.82 \pm 0.30 \text{ h}$  with a 95% CI (1.56, 2.08). Thereafter, its extraction did not significantly increase.

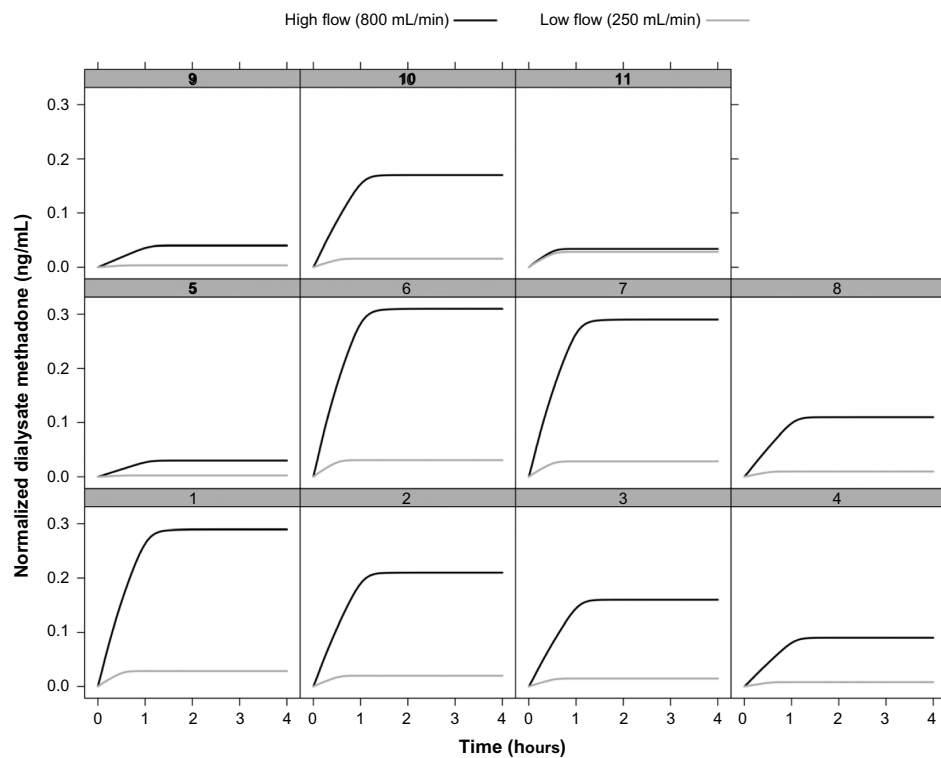
For each patient in Figure 3, methadone's  $u_1$  response to  $u_{1L}$  arrives at the right end ( $z = z_M$ ) at approximately 0.56 h, as in Figure 2. But due to methadone's mass transfer into the dialysate, the response is reduced so that the exiting  $u_1$  concentration,  $u_{1R}(t)$ , reaches  $0.824 \pm 0.013$  at  $t = 4 \text{ h}$ . As shown in Figure 3, just after  $t=0$ , methadone's  $u_2$  responses (gray curves) were immediate because the outflowing dialysate



**Figure 3** One-dimensional (1-D) ODE/PDE model's response with estimated mass transfers of methadone into dialysate.

**Note:** Although both solutions have the same normalized inflow values, their normalized outflow values are significantly different due to methadone's extraction.

**Abbreviations:** ODE, ordinary differential equation; PDE, partial differential equation.



**Figure 4** One-dimensional (1-D) ODE/PDE model's normalized methadone's response to its removal via the dialysate at low dialysate flow rates of 250 mL/min and high dialysate flow rates of 800 mL/min.

**Note:** Significant increase in methadone's mass transferred across the dialyzer membrane with the high dialysate flow rate.

**Abbreviations:** ODE, ordinary differential equation; PDE, partial differential equation.

“sees” the unit inflowing plasma methadone concentration at  $z=0$ . Notice also that the inflow methadone concentration into the dialysate,  $u_2(z = z_M, t)$ , is  $u_{2z_M} = 0$ ; so the outflow  $u_2$  at  $z=0$  is determined entirely by the plasma methadone concentration on the blood side of the membrane. At  $t = 4$  h, this outflowing normalized plasma methadone concentration,  $u_2(z = z_M, t)$ , reaches  $0.175 \pm 0.013$ .

For each patient, Figure 4 shows the plot of normalized methadone's removal via dialysate at low dialysate flow rates of 250 mL/min and high dialysate flow rates of 800 mL/min. The model revealed a significant increase in the change of methadone's mass transfer associated with the increase in dialysate flow rate,  $\% \Delta k_m = 18.56$ ,  $P = 0.02$ ,  $N = 11$ . The total amount of methadone mass transferred across the dialyzer membrane with high dialysate flow rate significantly increased ( $0.042 \pm 0.016$  versus  $0.052 \pm 0.019$  mg/kg,  $P = 0.02$ ,  $N = 11$ ). This was accompanied by a significant but small increase in methadone's mass transfer rate ( $0.113 \pm 0.002$  versus  $0.014 \pm 0.002$  mg/kg/h,  $P = 0.02$ ,  $N = 11$ ).

## Discussion

Our results show the ODE/PDE model (Figure 1) accurately predicted methadone's inflow and outflow plasma concentra-

tions as well as its E and T during dialysis. Results using the ODE/PDE model also showed methadone's removal was decreased at low dialysate flow rates compared to its removal at high dialysate flow rates. The ODE/PDE model suggested that methadone's reduced intradialytic removal was caused by a reduction in its mass transfer across the hemodialyzer membrane in a dialysate flow rate-dependent manner. This result was consistent with previous results that show increasing dialysate flow rate can give rise to an increase in mass transfer of low MW substances across dialyzer membranes,<sup>28,29</sup> and that increasing dialysate flow rate may increase the mass transfer of a highly protein-bound substance.<sup>30,31</sup>

While it is possible to qualitatively predict methadone's extent of removal during dialysis, our study aimed to advance a quantitative measure of methadone's removal. It is known that a few basic physicochemical properties of a drug govern the extent to which it is dialyzed: 1) MW, 2) apparent volume of distribution, 3) protein binding, 4) hydrophilicity, and 5) lipophilicity.<sup>32</sup> Molecules with low MW ( $< 500$  Da) are easily dialyzed, while higher MW compounds ( $> 1,000$ – $2,000$  Da) are not. In general, drugs with an apparent volume of distribution greater than 1 L/kg are poorly dialyzed. Drugs with

high protein binding, low water solubility, or that have high lipophilicity are also poorly dialyzed.<sup>32</sup>

Methadone has a low MW equal to 345.91 Da. It also has a high apparent volume of distribution with reported values in opioid addicts estimated as  $4.1 \pm 0.65$  L/kg in one study<sup>33</sup> and 2.1–5.61 L/kg in another.<sup>34</sup> Bootstrap population statistics give an apparent volume of distribution for methadone of  $5.5 \pm 0.89$  L/kg.<sup>35</sup> Methadone is highly bound to plasma proteins, particularly AAG.<sup>36</sup> Its plasma protein binding has been reported to be 60%–90%.<sup>37</sup> It is highly hydrophobic with a log 1-octanol:water partition coefficient ( $\log P_{o/w}$ ) of 4.762 at pH=7.4,<sup>38</sup> morphine's  $\log P_{o/w} = -0.10$ , oxycodone's  $\log P_{o/w} = 0.70$ , and codeine's  $\log P_{o/w} = 0.60$ .<sup>39</sup>  $\log P_{o/w} > 0$  characterizes hydrophobic substances soluble in the lipid phase, while  $\log P_{o/w} < 0$  typifies polar compounds soluble in the water phase.<sup>40</sup> Methadone is highly lipophilic as explained by its high  $\log P_{o/w}$ . Only the first property (small MW) supports that methadone is easily dialyzable. The other four properties indicate its removal by hemodialysis is reduced.

Our results showed that during low dialysate flow rates equal to the hemodialyzer's blood flow rates, low concentrations of methadone appeared in each patient's dialysate, compared to those during high dialysate flow rates. This finding objectively indicates methadone's dialyzability is low. Methadone clearance and extraction ratios have also been previously observed to be low in other studies.<sup>12,41</sup> But, the ODE/PDE model extends the concepts by providing quantitative measures of methadone's extent of dialyzability, including its mass transfer coefficient,  $k_m$ . Methadone's  $k_m$  allows quantitative estimation of the amount of methadone removed during hemodialysis.

If the objective is to determine the amount of methadone removed by dialysis, eg, to control dose replacement, estimation of  $k_m$  and the amount of methadone removed by dialysis may provide a better index for methadone dose replacement than dialysis clearance. Dialysis clearance has been found to correlate poorly with the fraction of drug in the body removed by hemodialysis.<sup>42</sup> Moreover, a drug's dialyzability cannot be predicted reliably from its MW, volume of distribution, or plasma protein binding.<sup>43</sup>

## Clinical application

The ODE/PDE model results can be applied as follows. Using a low dialysate flow rate of 250 mL/min, methadone's estimated removal during dialysis is  $j_{ME} = 0.013 \pm 0.002$  mg/kg/h, for a  $70 \pm 0.001$  kg patient. Then, methadone's removal rate with error during dialysis can be estimated as  $j_{ME} \times 70 \pm 0.001$  kg =  $0.90 \pm 0.14$  mg/h (95% CI: 0.67, 1.18). Thus, over the

4 h period of a dialysis session it is estimated that about  $3.6 \pm 0.56$  mg (95% CI: 2.5, 4.7) of methadone will be removed by hemodialysis in a 70 kg patient. The value of 3.01 mg calculated from the mass balance of measured values from Perlman et al<sup>12</sup> falls within that 95% CI.

The range of methadone concentrations from 100 ng/mL<sup>44</sup> to 400 ng/mL<sup>45</sup> are presumed to provide effective methadone maintenance. Yet other studies consider that effective maintenance depends on keeping serum methadone levels above 150–200 ng/mL during the 24 h interval between methadone doses.<sup>46–48</sup> In contrast, for pain treatment, methadone serum concentrations in opioid naïve patients range from 10 ng/mL to 80 ng/mL with a minimum lethal level of 670 ng/mL.<sup>49,50</sup> Notice that the ODE/PDE model's estimate of amount of methadone removed by dialysis translates into a plasma methadone concentration of about 11.96 ng/mL; since, concentration = amount/volume of distribution ( $V_d = 4.3$  L/kg  $\times$  70 kg = 301 L). Hence, while a plasma methadone concentration change of about 11.96 ng/mL seems modest, it may be sufficient to cause a lack of a sense of well-being in maintenance and chronic pain patients undergoing dialysis.<sup>51</sup> Especially, if levels fall 11.96 ng/mL below their minimum effective concentrations.

The aim of our study was not to examine the performance of a particular commercially available hemodialyzer or dialyzer membrane to remove methadone from blood. Therefore, we set the ODE/PDE model parameters to arbitrary, though realistic, values comparable to those of commercially available dialyzers.<sup>19,20</sup> Accordingly, interpretation of our results should be tempered with the understanding that they do not generalize to membranes with different characteristics, and hemodialysis prescriptions with different blood and dialysate flow rates. Nevertheless, given a specific membrane's characteristics, and a particular patient's hemodialysis prescription, initializing the ODE/PDE model with those parameter values is straightforward and will provide accurate results with little error comparable to those obtained in our study.

Drug to dialyzer–membrane binding has been demonstrated during continuous hemofiltration in the absence of protein.<sup>52</sup> The ODE/PDE model does not account for the possibility that methadone might bind to a dialyzer's membrane. Still, there is currently no factual evidence or anticipation that methadone does or should bind to dialyzer membranes. In addition, methadone is a neutral molecule with a formal charge of zero,<sup>53</sup> and thus is not expected to undergo cation exchange reactions with the dialyzer membrane.



Dialyzer reuse may cause a decrease in methadone's mass transfer due to a reduced number of dialyzer fiber bundles with associated loss of surface area. A reduction in the number of fiber bundles can either alter the membrane's diffusive properties or lead to a loss of hydraulic permeability<sup>32</sup> both of which could lead to a decline in methadone's mass transfer across the membrane. Although observations recorded during continuous hemodialysis indicate this decline is predictable, the role of membrane deposition of protein with reuse on the mass transfer across dialyzer membranes of low MW drugs, including methadone, is presently unknown.

It is known that some highly bound protein substances may be dialyzable when subjected to high dialysate flow rates.<sup>28</sup> We used this fact to test the model's ability to possibly detect an increase in methadone's dialyzability with increased dialysate flow. The ODE/PDE model predicted that methadone's dialyzability increases with high dialysate flow rates. Moreover, the model provided a quantitative estimate of methadone's removal during high dialysate flow.

We assumed methadone distributes in the whole blood compartment, while in reality the hematocrit fraction of dialyzer blood flow is not accessible to protein bound solutes like methadone. This means that to completely account for the hematocrit effect, the fraction of red cell volume available for dialysis ( $\gamma$ ) must be taken into account. This value is not known for methadone. For urea, it is 1.11. It is not 1 due to a reversibly bound pool of urea within red blood cells.<sup>54</sup> For creatinine  $\gamma$  is 0.50 and for phosphorus it is 0. Nevertheless, although  $\gamma$  is not known for methadone, it can be estimated as follows. The equation relating hematocrit to dialyzer blood flow is given by Sargent and Gotch:<sup>55</sup>

$$Q_{Bw} = Q_B [0.72\gamma(\text{HCT}) + 0.93(1 - \text{HCT})] \quad (1)$$

where  $Q_B$  is whole blood flow into the dialyzer,  $Q_{Bw}$  is blood water flow, HCT is the fractional red cell volume of whole blood (hematocrit: 45% men, 40% women), 0.93 is the water fraction of plasma, and 0.72 is the effective water fraction of the red cell.  $\gamma$  accounts for the hematocrit effect. Solving Equation 1 for  $\gamma$  gives:

$$\gamma = \frac{1.39[0.93(1 - \text{HCT} - 1)Q_B - Q_{Bw}]}{Q_B \text{HCT}} = 1.29 \quad (2)$$

for both men and women. Hence, methadone's hematocrit fraction of dialyzer blood flow is about 29%. In this sense, our results may represent predictable underestimates.

The Peclet number,  $Pe = (v_1 \times Z_M)/D = 347046.2$  for our model. Thus  $Pe \gg 100$ , which indicates we can neglect diffusion relative to convection because the system is strongly hyperbolic (convective).  $D$  denotes methadone's diffusivity equal to  $3.67 \times 10^{-6} \text{ cm}^2/\text{s}$  using the Stokes–Einstein equation with a plasma viscosity of 1.2 centipoise, where 1 centipoise =  $0.01 \text{ g/cm/s}$ .<sup>56</sup>

Finally, our experiments were not designed to detect the possibility that methadone could exhibit post-hemodialysis rebound resulting from equilibration between blood plasma and its tissue reservoir.<sup>57</sup> This could lead to a 10%–25% post-hemodialysis rebound of drug due to equilibration.<sup>32</sup> Therefore, sustained spillover of methadone into plasma from its tissue reservoir could (at least theoretically) cause a delayed toxic methadone concentration, particularly in acute poisoning. However, further studies are needed to determine the potential impact the interaction between inter-compartmental methadone equilibration and methadone spillover into plasma from tissue reservoirs could have on post-hemodialysis methadone concentrations. One approach would be to investigate inclusion of ODEs to model the delayed release and spillover.

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## Supplementary materials

Closely following Schiesser,<sup>1</sup> the blood methadone mass conservation balance gives:

$$\xi A \Delta z \frac{\partial u_1}{\partial t} = \xi A v_1 u_1|_z - \xi A v_1 u_1|_{z+\Delta z} + A_M \Delta z k_{M1} (u_2 - u_1) \quad (S1)$$

In Equation S1,  $\xi A \Delta z (\partial u_1 / \partial t)$  represents accumulation of methadone in an incremental volume of blood  $\xi A \Delta z$  (or depletion if the derivative in  $t$  is negative). The units of this term are  $(\text{cm}^2)(\text{cm})(\text{ng}/\text{cm}^3)(1/\text{min}) = \text{ng}/\text{min}$ .  $\xi A v_1 u_1|_z$  represents methadone's flow by convection into the incremental volume at  $z$ . The units of this term are  $(\text{cm}^2)(\text{cm}/\text{s})(\text{ng}/\text{cm}^3) = \text{ng}/\text{min}$ .  $-\xi A v_1 u_1|_{z+\Delta z}$  represents methadone's flow by convection into the incremental volume at  $z + \Delta z$ .  $+ A_M \Delta z k_{M1} (u_2 - u_1)$  represents methadone's mass balance between blood and dialysate into or out of the incremental volume at  $z$ . The units of this term are  $(\text{cm}^2/\text{cm})(\text{cm})(\text{cm}/\text{s})(\text{gmol}/\text{cm}^3) = \text{ng}/\text{min}$ . Note that methadone's mass transfer will be from blood to dialysate if  $u_1 > u_2$  as  $u_1$  decreases with  $t$ . Methadone's mass transfer coefficient  $k_m$  has units of  $\text{cm}/\text{min}$ . This coefficient presumes that only free methadone molecules pass through the dialyzer membrane and that bound methadone remains in the blood stream.

Dividing Equation S1 by  $\xi A \Delta z$  gives,

$$\frac{\partial u_1}{\partial t} = - \frac{v_1 u_1|_{z+\Delta z} - v_1 u_1|_z}{\Delta z} + \frac{A_M k_{M1}}{\xi A} (u_2 - u_1).$$

Taking the limit as  $\Delta z \rightarrow 0$ ,

$$\frac{\partial u_1}{\partial t} = - \frac{\partial(v_1 u_1)}{\partial z} + \frac{A_M k_{M1}}{\xi A} (u_2 - u_1) \quad (S2)$$

Equation S2 is the partial differential equation (PDE) for computing  $u_1(z, t)$ . We assume  $v_1$  is independent of  $z$  so that it can be taken outside the derivative in  $z$ .

The PDE for  $u_2$  follows from an analogous blood methadone mass conservation balance for the dialysate:

$$(1 - \xi) A \Delta z \frac{\partial u_2}{\partial t} = (1 - \xi) A v_2 u_2|_z - (1 - \xi) A v_2 u_2|_{z+\Delta z} + A_M \Delta z k_{M2} (u_2 - u_1).$$

Dividing by  $(1 - \xi) A \Delta z$  and taking the limit as  $\Delta z \rightarrow 0$  gives

$$\frac{\partial u_2}{\partial t} = - \frac{\partial(v_2 u_2)}{\partial z} + \frac{A_M k_{M2}}{(1 - \xi) A} (u_1 - u_2). \quad (S3)$$

Notice that the mass transfer terms in Equations S2 and S3 are opposite in sign indicating that the methadone that leaves the blood equals the methadone that enters the dialysate.

Equations S2 and S3 are first order in  $t$  and  $z$  (they are first order hyperbolic PDEs). Therefore, each requires an initial condition (IC) and a boundary condition (BC). The ICs are

$$u_1(z, t = 0) = f_1(z); u_2(z, t = 0) = f_2(z) \quad (S4)$$

The BCs are somewhat more complicated because of the entering and exiting blood volumes (these header volumes result from the dialyzer design). In each of these volumes, we assume perfect or complete mixing. Therefore, the blood methadone concentration in each volume is described by an ordinary differential equation (ODE) in  $t$  (variations in  $z$  do not occur through the perfect mixing assumption). The ODE for the left volume header is

$$\frac{V_{1L} du_1(z=0, t)}{dt} = q_1 (u_{1L}(t) - u_1(z=0, t)); u_1(z=0, t=0) = u_{10} \quad (S5)$$

where  $V_{1L}$  represents the left volume,  $q_1$  the blood volumetric flow rate,  $u_{1L}$  the inlet methadone blood concentration, and  $u_{10}$  the initial condition for  $u_1(z=0, t)$  at  $t=0$ .

Also, the right header volume is described by the following ODE:

$$\frac{V_{1R} du_{1R}(t)}{dt} = q_1 (u_1(z=z_M, t) - u_{1R}(t)); u_{1R}(t=0) = u_{1R0}, \quad (S6)$$

which gives the outflow blood methadone concentration  $u_{1R}(t)$ . Note that the input into S6 is the outflow blood methadone concentration  $u_1(z=z_M, t)$  from Equation S2;  $z_M$  is the length of the dialyzer membrane. Equation S6 is an ODE in addition to the PDEs of Equations S2 and S3. In addition,  $q_1 = v_1 \xi A$  relates the blood volumetric and linear flow rates.

The BC for Equation S3 is

$$u_2(z=z_M, t) = g_2(t), \quad (S7)$$

where  $g_2(t)$  is a prescribed function. Equations S2 to S7 constitute the ODE/PDE equations of the model for our in silico experiments using the model.

The ODE/PDE model for the dialyzer is first order in  $t$  (convective, hyperbolic), and since it models convection, it naturally propagates steep fronts (even discontinuities) which makes its numerical solution relatively difficult. However, we designed methadone mass flux limiters for this situation to eliminate numerical distortions such as oscillations.<sup>2</sup>

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