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Thermodynamic Considerations in Solid Adsorption of Bound Solutes for Patient Support in Liver Failure

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Abstract

New detoxification modes of treatment for liver failure that use solid adsorbents to remove toxins bound to albumin in the patient bloodstream are entering clinical evaluations, frequently in head-to-head competition. While generally effective in reducing toxin concentration beyond that obtainable by conventional dialysis procedures, the solid adsorbent processes are largely the result of heuristic development. Understanding the principles and limitations inherent in competitive toxin binding, albumin versus solid adsorbent, will enhance the design process and, possibly, improve detoxification performance. An equilibrium thermodynamic analysis is presented for both the Molecular Adsorbent Recirculating System (MARS) and Fractionated Plasma Separation, Adsorption, and Dialysis System (Prometheus), two advanced systems with distinctly different operating modes but with similar equilibrium limitations. The Prometheus analysis also applies to two newer approaches: sorbent suspension reactor (SSR) and microspheres-based detoxification system (MDS). Primary results from the thermodynamic analysis are that: (1) the solute-albumin binding constant is of minor importance to equilibrium once it exceeds about 10^5 L mol^{-1} ; (2) the Prometheus approach requires larger solid adsorbent columns than calculated by adsorbent solute capacity alone; and (3) the albumin-containing recycle stream in the MARS approach is a major reservoir of removed toxin. A survey of published results indicates that MARS is operating under mass transfer control dictated by solute-albumin equilibrium in the recycle stream and Prometheus is approaching equilibrium limits under current clinical protocols.

Acute liver failure (ALF), defined as sudden onset with no previous history of liver disease, and acute-on-chronic liver failure (AcLF), resulting from sudden decompensation of existing liver disease, are life-threatening conditions that have poor prognosis^{1, 2}. Despite differences in cause and pathophysiology of the underlying disease state, clinical presentation of the disease and its progression are similar, e.g., advancing encephalopathy, blood coagulopathy, elevated ammonia, lactate, and bilirubin levels, and frequently include hemodynamic instability, renal failure, and respiratory distress³. Hence standard medical therapy, primarily supportive in nature, is the same for both ALF and AcLF.

Detoxification approaches have been developed for treatment of liver failure based upon the premises that (1) liver failure progresses because of the presence of toxic substances that continue to promote liver cell death; (2) removal of many toxic substances is problematic because the toxins bind tightly to proteins, such as albumin, limiting free solute concentration in the plasma, which in turn, severely limits the ability of conventional dialysis to remove the toxins; and (3) detoxification, i.e. removal of toxins, will allow the liver to exercise its regenerative capabilities, promoting recovery from liver failure. The

detoxification approaches generally use one or more high affinity binders that can successfully compete with albumin to remove albumin-bound toxins. Based upon operating characteristics, detoxification approaches can be broadly classified into two categories: open-loop, in which the high affinity binder is continuously added and removed from the system, and closed-loop, in which toxins accumulate on binder without removal of binder from the system.

The HemoCleanse-DT (formerly known as the Biologic-DT and Liver Dialysis Unit, HemoCleanse, Lafayette, IN) and single pass albumin dialysis (SPAD) are examples of open-loop dialysis systems based on adding a high affinity binder to the dialysate. The HemoCleanse-DT uses a finely divided, high surface area charcoal adsorbent as the toxin binder while SPAD uses albumin. Perfusion with the HemoCleanse-DT resulted in normalization of blood chemistries (clearance of aromatic amino acids, bilirubin, ammonia, and cytokines and increase in Fischer amino acid ratio), reduction in encephalopathy, and improvement in physiologic status in several small clinical studies^{4–7}. However, the number of patients in any of the studies was insufficient to draw conclusions with respect to efficacy. Although no clinical trials of SPAD have been reported, several case reports have found significant removal of copper from a Wilson's disease patient⁸, reductions in hepatic encephalopathy and bilirubin⁹, and no significant difference between 1.85% and 5.0% dialysate albumin concentration in bilirubin removal from a patient with hyperbilirubinemia¹⁰. Modeling predictions indicate that albumin concentrations as low as 0.5% would have been equally effective for these cases^{11–13}.

The Molecular Adsorbent Recirculating System (MARS, Gambro AB, Stockholm, Sweden) and Fractionated Plasma Separation, Adsorption, and Dialysis System (Prometheus, Fresenius AG, Bad Homburg, Germany) are examples of closed-loop systems. MARS uses an intermediate albumin dialysis step to transfer toxins from albumin in the plasma to solid adsorbents while Prometheus directly contacts the adsorbents with plasma. Regardless, the solid adsorbents remain in the system during patient perfusion.

MARS perfusion has been used in over 4000 ALF or AcLF patients¹⁴ and is associated with significant clearance of bilirubin, bile acids, ammonia, and cytokines and reduction in encephalopathy^{15–18}. The most recent entry into clinical evaluations, Prometheus has been associated with reduction in cerebral edema¹⁹, and reductions in albumin-bound toxins such as bilirubin, bile acids, and cholinesterase^{20–23}. Although neither MARS nor Prometheus have not yet been shown to have clinical efficacy with respect to patient survival in an appropriately controlled, randomized study, several reports of direct comparison between the systems in support of liver failure patients have appeared^{24–27}. The reports indicate that both MARS and Prometheus remove albumin-bound toxins with slight differences in the removal of different toxins.

Although both MARS and Prometheus are based upon the well-founded principle that albumin-bound toxins in plasma, which are not amenable to removal by conventional dialysis, can be removed by providing another, preferably higher affinity, binder for the toxins, design and development of the two approaches have been largely heuristic in nature. The present work presents a thermodynamic analysis of the equilibrium limits of the two closed-loop systems in order to gain greater understanding the governing parameters that limit their ultimate ability to remove albumin-bound toxins from plasma. Better understanding of the governing parameters should result in improved systems for clinical use.

Theory

A simplified schematic of the closed-loop portion of the Prometheus system is shown in Fig 1A. Blood from the patient passes through a proprietary plasma filter where a fraction of the plasma flow is removed and passed through two proprietary solid adsorbent cartridges, one containing a neutral resin and the other containing an ion exchange resin. In each cartridge, albumin-bound solutes in the plasma can dissociate from the albumin to the free solute form which, in turn, can either recombine with the albumin or bind with the solid adsorbent as depicted in Fig 1B. Plasma effluent from the cartridges is returned to the blood stream. The actual Prometheus system passes the blood stream through high flux dialysis before return to the patient. Because the high flux dialysis is used for removal of water soluble species and water volume rather than albumin-bound solutes, it is not shown in order to emphasize the relevant aspects of albumin-solute-adsorbent transfer and equilibrium.

As depicted in Fig 2A, the MARS approach uses a proprietary cartridge that is impermeable to albumin to effect transfer of albumin-bound solutes in the blood stream to an albumin-containing recycle stream. The recycle stream is then passed through two proprietary cartridges, one containing charcoal and the other containing an anion exchange resin, to scavenge bound solutes from the recycle circuit. The individual steps for bound solute removal are depicted in Fig 2B. Since the MARS-flux membrane is impermeable to albumin, solute must dissociate to the free solute form for transit across the membrane. Solute then associates with albumin in the recycle circuit and is carried to the adsorbent cartridges where it must again dissociate from albumin in order to bind with the solid adsorbent. A secondary low flux dialysis cartridge in the recycle circuit, that is used to remove water soluble species and water volume, has been omitted from the diagram in order to focus on bound-solute transfer and equilibrium.

Irrespective of system operating parameters, i.e., blood flow rates, plasma flow rates, recycle circuit flow rates, the maximum removal of albumin-bound solutes from the patient plasma is dictated by equilibrium considerations: maximum removal is achieved when the free solute concentration is in equilibrium with albumin concentrations and adsorbent concentrations in the patient, recycle circuit, and adsorbent cartridges. This simple statement can be used to develop equations that are useful not only for understanding results from current clinical evaluations but for improved system design.

Equations common to both Prometheus and MARS

Solute-binder equilibrium equations that apply to both patient plasma and the recycle stream, with appropriate subscripting, are (see nomenclature section for symbol definitions)

solute-binder equilibrium :

$$K_B = \frac{(C_{S \bullet B})_e}{(C_S)_e (C_{\bullet B})_e} \quad [1]$$

total binder mole balance :

$$(C_B^t) = (C_{\bullet B}) + (C_{S \bullet B}) \quad [2]$$

total solute mole balance :

$$(C_S^t) = (C_S) + (C_{S \bullet B}) \quad [3]$$

Eq [1], Eq [2], and Eq [3] can be combined to produce
equilibrium total solute concentration :

$$(C_s^t)_e = \frac{\{1 + K_B[(C_s)_e + (C_B^t)]\} (C_s)_e}{[1 + K_B(C_s)_e]} \quad [4]$$

Likewise, solute-adsorbent equations that apply to adsorbent in equilibrium with either patient plasma or the recycle stream, with appropriate subscripting, are

solute-adsorbent equilibrium :

$$K_Q = \frac{q_e}{(C_s)_e (q^*)_e} \quad [5]$$

adsorbent site balance :

$$q_{\max} = (q^*) + q \quad [6]$$

Eq [5] and Eq [6] can be combined to produce the familiar Langmuir adsorption isotherm
equilibrium adsorbed solute :

$$q_e = \frac{q_{\max} (C_s)_e}{[(K_Q)^{-1} + (C_s)_e]} \quad [7]$$

The metric for process efficiency, independent of process, is defined as the fractional reduction in plasma solute concentration :

$$\varphi = \frac{(C_s^t)_{p,0} - (C_s^t)_{p,e}}{(C_s^t)_{p,0}} \quad [8]$$

Combining Eq [4] and Eq [8] and using the quadratic formula produces an expression for the equilibrium free solute concentration in the plasma :

$$(C_s)_{p,e} = \frac{-b + \sqrt{b^2 + 4K_B(1 - \varphi)(C_s^t)_{p,0}}}{2K_B} \quad [9]$$

$$\text{where } b = \left\{ 1 + K_B[(C_B^t)_p - (1 - \varphi)(C_s^t)_{p,0}] \right\}$$

Prometheus performance equations

A mole balance on total solute in the plasma plus total solute on the adsorbent yields

$$(C_s^t)_{p,e} V_p + (q_e) m_Q = (C_s^t)_{p,0} V_p \quad [10]$$

Eq [10] can be rearranged and combined with Eq [7] and Eq [8] to produce an equation for fractional reduction of total solute plasma concentration as a function of the Prometheus system design parameters,

$$\varphi = \left[\frac{m_Q q_{\max}}{V_p (C_s^t)_{p,0}} \right] \left[\frac{(C_s)_{p,e}}{[(K_Q)^{-1} + (C_s)_{p,e}]} \right] \quad [11]$$

where $(C_s)_{p,e}$ is given by Eq [9]. Root finding techniques must be used to solve Eq [11] because $(C_s)_{p,e}$ is also a (nonlinear) function of φ through Eq [9].

MARS performance equations

A mole balance on total solute in the plasma plus total solute in the recycle stream plus total solute on the adsorbent yields

$$(C_s^t)_{p,e} V_p + (C_s^t)_{r,e} V_r + (q_e) m_Q = (C_s^t)_{p,0} V_p \quad [12]$$

Eq [12] can be rearranged and combined with Eq [4], [7] and [8] to produce an equation for fractional reduction of total solute plasma concentration as a function of the MARS system design parameters,

$$\varphi = \left[\frac{m_Q q_{\max}}{V_p (C_s^t)_{p,0}} \right] \left[\frac{V_r \{1 + K_B [(C_s)_{r,e} + (C_B^t)_r]\} (C_s)_{r,e}}{(m_Q q_{\max}) [1 + K_B (C_s)_{r,e}]} + \frac{(C_s)_{r,e}}{[(K_Q)^{-1} + (C_s)_{r,e}]} \right] \quad [13]$$

At equilibrium, the free solute concentration in the plasma and recycle stream are equal, i.e.,

$$(C_s)_{p,e} = (C_s)_{r,e} \quad [14]$$

so $(C_s)_{r,e}$ can be calculated using Eq [9]. Again, root finding techniques must be used to solve Eq [13] because $(C_s)_{r,e}$ is also a (nonlinear) function of φ .

Results

System design parameters for bound-solute/solid adsorption include those that can be classified as patient parameters ($(C_B^t)_p$, V_p , $(C_s^t)_{p,0}$, and K_B) and those that can be classified as solid adsorbent parameters (m_Q , $q_{\max}$, and K_Q). Two parameters that will be considered relatively constant in the following analysis are the patient plasma albumin concentration, $(C_B^t)_p$ (30 g/L is typical for liver failure patients), and the patient distribution volume for bound-solute, V_p (taken as the patient plasma volume, ~3.0 L). The design/performance question then becomes: what mass of adsorbent (m_Q), with associated solute binding parameters, $q_{\max}$ and K_Q , is required to achieve a specified fractional reduction in patient bound-solute concentration (φ) for a bound-solute initially present at concentration $(C_s^t)_{p,0}$ with an albumin-binding constant of K_B ?

Both fractional reduction expressions, Eq [11] and Eq [13], have a natural, dimensionless parameter

$$\chi = \left[\frac{m_Q q_{\max}}{V_p (C_s^t)_{p,0}} \right] \quad [15]$$

that is the ratio of total adsorption capacity of the solid ($m_Q q_{\max}$) to the total amount of solute present in the patient at the start of perfusion, i.e., χ reflects the solid adsorbent equivalents in the system. Another dimensionless parameter, K_{rat} ($= K_Q/K_B$), describes the relative affinity of the solute for solid adsorbent versus albumin. Parametric plots of ϕ versus χ as (1) a function of K_B and $(C_s^t)_{p,0}$ at constant K_{rat} and (2) a function of K_B and K_{rat} at constant $(C_s^t)_{p,0}$ are useful in both design of a closed-loop adsorption system and in interpretation of perfusion results in actual application.

Specification of an adsorbent solid mass or volume for a system is equivalent to specification of $\chi_{perfusion}$, which is the adsorbent equivalents available for treatment of a patient. In contrast with the adsorbent mass in the system, which remains constant, $\chi_{perfusion}$ will vary from patient to patient. A clinical time trajectory on a (χ, ϕ) plot will be a vertical line starting at $\phi = 0$ and $\chi = \chi_{perfusion}$. Fractional reduction above the equilibrium curve is not possible with solid adsorption only. The rate of fractional reduction is dependent upon the distance of the current (χ, ϕ) operating point from the equilibrium curve. Hence, the maximum rate of fractional reduction will always occur at the start of perfusion because the operating point is farthest from the equilibrium curve. Likewise, the rate of fractional reduction will decrease with time as the system moves toward the equilibrium curve. Sufficiently close approach of the (χ, ϕ) operating point to the equilibrium curve will reduce the rate of fractional reduction to zero.

In contrast with the ready availability of albumin-solute binding data, values for $q_{\max}$ and K_Q for various solutes and solid adsorbents pertinent to putative liver failure toxins are not generally available. Ash28 has published bilirubin adsorption data for three activated carbon sorbents. When corrected for free concentration, as opposed to total concentration, the adsorbent parameters are: Maxsorb granules ($q_{\max} = 1.19 \times 10^{-7}$ mol/g, $K_Q = 8.68 \times 10^7$ L mol $^{-1}$); Maxsorb powder ($q_{\max} = 4.06 \times 10^{-6}$ mol/g, $K_Q = 8.06 \times 10^6$ L mol $^{-1}$) and Norit powder ($q_{\max} = 1.59 \times 10^{-5}$ mol/g, $K_Q = 2.61 \times 10^7$ L mol $^{-1}$). Using $K_B = 6.5 \times 10^6$ L mol $^{-1}$ for the albumin-bilirubin binding constant²⁹, values of K_{rat} range from 1.2 to 13. Data for cholic acid ($q_{\max,CA} = 4.97 \times 10^{-4}$ mol/g, $K_{Q,CA} = 2.84 \times 10^5$ L mol $^{-1}$, $K_{B,CA} = 3 \times 10^3$ L mol $^{-1}$)^{27, 30} and deoxycholic acid ($q_{\max,CDCA} = 5.51 \times 10^{-4}$ mol/g, $K_{Q,CDCA} = 3.5 \times 10^5$ L mol $^{-1}$, $K_{B,CDCA} = 5.5 \times 10^4$ L mol $^{-1}$)^{27, 30} adsorption on activated carbon yield values of $K_{rat,CA} \sim 95$ and $K_{rat,CDCA} \sim 6.4$. Thus, K_{rat} ranges of 1 to 100 will be used to illustrate the impact of K_{rat} on fractional reduction at equilibrium.

Prometheus perfusion

A parametric plot of fractional reduction versus adsorbent equivalents for a range of solute-albumin binding constant, K_B (10^3 , 10^5 , and 10^7 L mol $^{-1}$), and K_{rat} (1, 10, and 100) at initial total solute concentration, $(C_s^t)_{p,0} = 0.25$ mmol L $^{-1}$, is presented in Fig 3. The parity line, $\phi = \chi$, represents the absolute minimum amount of solid adsorbent required to achieve a specified fractional reduction. The parity line is based upon a $q_{\max}$ specification only and reflects $K_{rat} = \infty$, i.e., a solid adsorbent with infinitely higher affinity for the solute than albumin. In practice, because $K_{rat} \ll \infty$, more solid adsorbent than that predicted by $q_{\max}$ alone will be required.

The fractional reduction versus adsorbent equivalents equilibrium curves depicted in Fig 3 shift upward and to the left with either increasing K_{rat} or K_B . As might be expected, less adsorbent equivalents are required to achieve a specified fractional reduction as K_{rat} increases because the solid has greater affinity for the solute (at same binding capacity). More counterintuitive are the increasing fractional reduction with increasing K_B at the same K_{rat} and the near superposition of the curves for $K_B = 10^5$ and 10^7 L mol⁻¹ for all values of K_{rat} . In the first case, increasing K_B implies proportionately increasing K_Q and, through Eq [11], a smaller denominator in the expression for ϕ . The latter result is a reflection of increasingly negligible free solute concentrations as K_B increases.

As depicted in Fig 4, which is a plot at constant $K_{rat} = 10$ with varying initial total solute concentration, $(C_s^t)_{p,0}$ (0.05, 0.25, and 0.50 mmol L⁻¹), and albumin binding constant, K_B (10^3 , 10^5 , and 10^7 L mol⁻¹), fractional reduction is highly dependent upon the initial total solute concentration. Equilibrium curves at constant K_B shift to the left with increasing $(C_s^t)_{p,0}$ and to the right with decreasing $(C_s^t)_{p,0}$ because $(C_s^t)_{p,0}$ appears in the denominator of adsorbent equivalents, Eq [15]. The curves also shift upward with increasing $(C_s^t)_{p,0}$ and downward with decreasing $(C_s^t)_{p,0}$ at constant χ , reflecting the effect of increasing or decreasing, respectively, free solute concentration at equilibrium.

Clinical perfusion results^{26, 27} for fractional reduction of cholic acid (CA, $(C_s^t)_{p,0} = 0.025$ mmol L⁻¹, $K_{B,CA} = 3 \times 10^3$ L mol⁻¹), chenodeoxycholic acid (CDCA, $(C_s^t)_{p,0} = 0.080$ mmol L⁻¹, $K_{B,CDCA} = 5.5 \times 10^4$ L mol⁻¹), and bilirubin ($(C_s^t)_{p,0} = 0.513$ mmol L⁻¹, $K_{B,bili} = 6.5 \times 10^6$ L mol⁻¹) are depicted in Figs 5A, 5B, and 5C, respectively. The shaded region represents the range in fractional reduction observed from clinical perfusion. Fractional reduction of all three species, CA ($K_{rat,CA} \sim 95$), CDCA ($K_{rat,CDCA} \sim 6.4$), and bilirubin ($K_{rat,bili} \sim 1.2$ to 13) is consistent with Prometheus operating in a mass transfer limited regime. The fractional reduction may be approaching an equilibrium limited regime for CA and CDCA, depending upon the actual K_Q and q_{max} for the solid adsorbent. This is consistent with the observation that rates of CA and CDCA removal approach zero toward the end of a clinical perfusion²⁷. In contrast, the likely (χ, ϕ) operating point remains well below the equilibrium curves for bilirubin, which is consistent with decreasing, but nonzero, rates of fractional bilirubin reduction at the end of a clinical perfusion²⁶.

MARS perfusion

Additional MARS parameters include V_r and $(C_B^t)_r$, the volume and albumin concentration, respectively, in the recycle stream. The MARS recycle stream volume, V_r , is taken as 600 mL²⁴ and varying recycle stream albumin concentrations are considered. A parametric plot of fractional reduction versus adsorbent equivalents for a range of solute-albumin binding constant, K_B (10^3 , 10^5 , and 10^7 L mol⁻¹), and K_{rat} (1, 10, and 100) at initial total solute concentration, $(C_s^t)_{p,0} = 0.25$ mmol L⁻¹, and recycle stream albumin concentration, $(C_B^t)_r = 150$ g L⁻¹, is presented in Fig 6. The most striking feature in Fig 6 is the initially steep rise in fractional reduction at low adsorbent equivalents that is due to the presence of albumin, a major solute binder, in the recycle stream. Similar to Prometheus, fractional reduction versus adsorbent equivalents curves shift upward and to the left with either increasing K_{rat} or K_B . Also similar is the near superposition of the curves for $K_B = 10^5$ and 10^7 L mol⁻¹ for all values of K_{rat} .

The effects of variations in albumin concentration in the recycle stream, $(C_B^t)_{p,r}$ (100, 150, and 200 g L⁻¹), and initial total solute concentration, $(C_s^t)_{p,0}$ (0.05, 0.25, and 0.50 mmol L⁻¹), at constant $K_B = 10^5$ L mol⁻¹ and $K_{rat} = 10$ are displayed in Fig 7. The height of the initial steep rise in fractional reduction increases with increasing $(C_B^t)_{p,r}$, reflecting a larger available “sink” for the solute. Fractional reduction approaches an asymptote with respect to adsorbent equivalents that depends upon the initial total solute concentration and that is independent of albumin concentration in the recycle stream. The actual asymptote value, however, is dependent upon K_B and K_{rat} .

Clinical perfusion results^{26, 27} for fractional reduction of CA, CDCA, and bilirubin are depicted in Figs 8A, 8B, and 8C, respectively. The shaded region represents the range in fractional reduction observed from clinical perfusion. Fractional reduction of CA is above the equilibrium associated with albumin binding in the secondary circuit and below the equilibrium associated with solid adsorption. Since CA has relatively low binding affinity for albumin, the fractional reduction may reflect significant removal through the secondary dialysis cartridge. Both CDCA and bilirubin fractional reduction reflect mass transfer limitation associated with presence of free CDCA and bilirubin in the recycle stream, which acts to reduce the primary driving force for removal from the patient^{11, 12}.

Discussion

The Langmuir isotherm, Eq [7], relates solid-solute adsorption, q , to free solute concentration in the surrounding media, (C_s) , with two solid adsorbent parameters, q_{max} and K_Q , that characterize the adsorbent properties of a material. These solid adsorbent parameters are typically determined by regression of a linearized version of Eq [7], e.g., Lineweaver-Burke, against experimental data. Care must be taken in the regression to use the *free* solute concentration since use of total solute concentration in the presence of competitive liquid phase binder for the solute, such as albumin, will tend overestimate q_{max} and underestimate the true K_Q by orders of magnitude.

A major design consideration in use of solid adsorbents for treatment of liver failure is the amount of adsorbent required to effect a clinically significant reduction in bound-solute concentration in the patient. As illustrated in Fig 3, Fig 4, Fig 6, and Fig 7, using q_{max} alone, which is equivalent to the parity line $\phi = \chi$, is valid only in the absence of competitive binding ($K_{rat} \rightarrow \infty$). Better estimation of the minimum adsorbent requirement requires construction of the appropriate fractional reduction versus adsorbent equivalents curve using the equations presented here.

Minimum adsorbent column volume can be calculated from the minimum adsorbent requirement using the packing density of the adsorbent. The solids void fraction can then be used to estimate the plasma or recycle stream volume in the solid adsorbent column. Columns sized in this manner are easily incorporated into the MARS approach because the volume of the recycle stream can increase as column volume increases. Adsorbent column volume in the Prometheus approach, however, has an alternative maximum dictated not by clinical objective in bound solute concentration reduction, but by the total extracorporeal volume that a patient can tolerate, about 1 L. The total extracorporeal volume includes both the plasma in the adsorbent column and the hemodialysis circuit. The alternative maximum adsorbent column volume could be less than the minimum volume calculated by the clinical objective in bound solute concentration reduction.

A major limitation of a thermodynamic analysis is that it cannot predict actual rates at which equilibrium is approached. Thermodynamic analysis can be used, however, to

retrospectively determine whether equilibrium limits were approached in actual practice. All bound-solute detoxification processes will initially operate in a mass transfer limited mode that is governed by concentration differences and mass transfer characteristics. In essence, the (χ, ϕ) operating point is below the equilibrium curve. As time passes, the (χ, ϕ) operating trajectory will approach the equilibrium curve and the process will become equilibrium limited through loss of the concentration difference driving force. Design of a detoxification system for clinical use is a delicate balance between achievable mass transport rates, which depend highly upon concentration differences and moderately on fluid flow rates, patient hemodynamic stability and achievable blood draw rates, and desired target fractional reduction in toxins over a specified duration of perfusion. Current clinical practice is a six-hour perfusion^{22, 24, 25, 27, 31}.

General observations that result from this analysis for both Prometheus and MARS perfusion are: (1) fractional reduction of solutes present at low concentration is difficult, regardless of solute-albumin binding constant, K_B , because the free solute concentration is inherently low; (2) fractional reduction of solutes with low albumin-binding constant is improved through the dialysis circuits that both approaches use; and (3) fractional reduction of solutes with solute-albumin binding constants greater than about 10^5 L mol^{-1} will be comparable. Observations that bile acid clearance dropped toward zero at the end of the six-hour perfusion²⁷ are indicative of bile acid removal approaching equilibrium limits. Likewise, observations that bilirubin clearance was decreasing but still significant at the end of six hours are indicative that bilirubin removal remains in the mass transfer control regime under the clinical perfusion protocol²⁶.

Additionally, MARS perfusion appears to be mass transfer limited in fractional reduction because of the albumin in the recycle circuit. Incomplete transfer of solute from the recycle circuit albumin to the solid adsorbent results in solute (and free solute) being carried back to the primary separation cartridge. Free solute present in the recycle stream reduces the rate at which solute can transfer across the membrane because the driving force for transfer is the free solute concentration difference across the membrane. The presence of albumin in the recycle circuit also limits effective use of the solid adsorbent (Fig 7). While more effective solid adsorbent use comes with reduced albumin concentration in the recycle circuit, a price is paid in rate: lower albumin concentrations result in higher free solute concentrations which, in turn, reduces the driving force for removal in the primary separation cartridge.

The equilibrium analysis presented for Prometheus applies equally to two new solid adsorption approaches: the sorbent suspension reactor (SSR)²⁸ and microspheres-based detoxification system (MDS)³². While the patient plasma and solid adsorbents for these systems are in different compartments, the solute distribution is similar to that depicted in Fig 1B with the proviso that free solute concentration in the plasma is equal to free solute concentration in the solid adsorbent compartment at equilibrium. Additionally, both SSR and MDS are likely to be mass transfer limited (especially since the amount of solid adsorbent in the system is, in principle, unlimited) for the same reason that MARS appears mass transfer limited: the driving force for transfer across the primary membrane is the free solute concentration difference across the membrane. Even highly adsorbent solids will have a free solute concentration associated with the adsorption process.

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Nomenclature

b	parameter in Eq [9], dimensionless
(C_b^t)	total binder (albumin) concentration, mol L ⁻¹
$(C_{\bullet B})$	free binder (albumin) concentration, mol L ⁻¹
(C_s^t)	total solute concentration, mol L ⁻¹
(C_s)	free solute concentration, mol L ⁻¹

$(C_{S \cdot B})$	bound solute concentration, mol L ⁻¹
K_B	solute-binder binding constant, L mol ⁻¹
K_{rat}	binding constant ratio ($= K_B/K_Q$), dimensionless
K_Q	solute-adsorbent binding constant, L mol ⁻¹
m_Q	mass of solid adsorbent, g
q	adsorbent solute loading, mol g ⁻¹
q^*	adsorbent free binding site concentration, mol g ⁻¹
q_{max}	adsorbent solute capacity, mol g ⁻¹
V	volume, L
χ	adsorbent equivalents, dimensionless
ϕ	fractional solute reduction in patient, dimensionless subscripts
e	equilibrium
p	plasma
r	recycle stream
0	initial condition

Fig 1. Schematic of Prometheus perfusion. (A) Circuit diagram. (B) Solute transfer from plasma binder to solid adsorbent.

Fig 2.
Schematic of MARS perfusion. (A) Circuit diagram. (B) Solute transfer from plasma binder to solid adsorbent.

Fig 3.

Fractional reduction versus adsorbent equivalents at equilibrium for Prometheus perfusion at initial total solute concentration, $(C_s^t)_{p,0} = 0.25 \text{ mmol L}^{-1}$, with solid/albumin binding constant ratio, K_{rat} , as shown. Heavy solid lines: $K_B = 10^3 \text{ L mol}^{-1}$; light solid lines: $K_B = 10^5 \text{ L mol}^{-1}$; light dotted lines $K_B = 10^7 \text{ L mol}^{-1}$; heavy dashed line: parity $\phi = \chi$.

Fig 4.

Fractional reduction versus adsorbent equivalents at equilibrium for Prometheus perfusion at solid/albumin binding constant ratio, $K_{rat} = 10$, and initial total solute concentration, $(C_s^t)_{p,0}$, as shown. Heavy solid lines: $K_B = 10^3 \text{ L mol}^{-1}$; light solid lines: $K_B = 10^5 \text{ L mol}^{-1}$; light dotted lines $K_B = 10^7 \text{ L mol}^{-1}$; heavy dashed line: parity $\phi = \chi$.

Fig 5.

Fractional reduction versus adsorbent equivalents at equilibrium under clinical Prometheus perfusion conditions^{26, 27} at values of K_{rat} as shown. Heavy dashed line: parity $\phi = \chi$. Gray shaded area clinically observed fractional reduction range. (A) CA, $(C_s^t)_{p,0} = 0.025 \text{ mmol L}^{-1}$, $K_{B,CA} = 3 \times 10^3 \text{ L mol}^{-1}$. (B) CDCA, $(C_s^t)_{p,0} = 0.080 \text{ mmol L}^{-1}$, $K_{B,CDCA} = 5.5 \times 10^4 \text{ L mol}^{-1}$. (C) Bilirubin, $(C_s^t)_{p,0} = 0.513 \text{ mmol L}^{-1}$, $K_{B,bili} = 6.5 \times 10^6 \text{ L mol}^{-1}$.

Fig 6.

Fractional reduction versus adsorbent equivalents at equilibrium for MARS perfusion at initial total solute concentration, $(C_s^t)_{p,0} = 0.25 \text{ mmol L}^{-1}$, and recycle stream albumin concentration, $(C_B^t)_r = 150 \text{ g L}^{-1}$, with solid/albumin binding constant ratio, K_{rat} , as shown. Heavy solid lines: $K_B = 10^3 \text{ L mol}^{-1}$; light solid lines: $K_B = 10^5 \text{ L mol}^{-1}$; light dotted lines $K_B = 10^7 \text{ L mol}^{-1}$; heavy dashed line: parity $\phi = \chi$.

Fig 7.

Fractional reduction versus adsorbent equivalents at equilibrium for MARS perfusion at constant $K_B = 10^5 \text{ L mol}^{-1}$ and $K_{rat} = 10$, with initial total solute concentration, $(C_s^t)_{p,0}$, as shown. Heavy solid lines: $(C_b^t)_r = 100 \text{ g L}^{-1}$; light solid lines: $(C_b^t)_r = 150 \text{ g L}^{-1}$; light dotted lines $(C_b^t)_r = 200 \text{ g L}^{-1}$; heavy dashed line: parity $\phi = \chi$.

Fig 8.

Fractional reduction versus adsorbent equivalents at equilibrium under clinical MARS perfusion conditions^{26, 27} at values of K_{rat} as shown. Heavy dashed line: parity $\phi = \chi$. Gray shaded area clinically observed fractional reduction range. (A) CA, $(C_s^t)_{p,0} = 0.025 \text{ mmol L}^{-1}$, $K_{B,CA} = 3 \times 10^3 \text{ L mol}^{-1}$ (B) CDCA, $(C_s^t)_{p,0} = 0.080 \text{ mmol L}^{-1}$, $K_{B,CDCA} = 5.5 \times 10^4 \text{ L mol}^{-1}$. (C) Bilirubin, $(C_s^t)_{p,0} = 0.513 \text{ mmol L}^{-1}$, $K_{B,billi} = 6.5 \times 10^6 \text{ L mol}^{-1}$.