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Review of the Application of Kirchhoff's Laws of Series and Parallel Flows to Pharmacology: Defining Organ Clearance

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Abstract

Dosing rate decisions for drugs and changes in dosing in a patient due to disease states, drug interactions and pharmacogenomics are all based on clearance, a measure of the body's ability to eliminate drug. The primary organs of elimination are the liver and the kidney. Clearance for each of these organs is a summative composition of biologic processes. In 1857, Gustav Kirchhoff first developed his laws to describe the "motion of electricity in conductors... [and] ...in wires", recognizing that summative processes occur either in parallel or in series. Since then, Kirchhoff's Laws have also been applied to heat transfer, diffusion and drag force on falling objects, but not to pharmacology. Although not previously recognized, renal clearance always follow Kirchhoff's Laws, as does hepatic clearance for drugs where basolateral transporters are not clinically relevant. However, when basolateral transporters are clinically relevant, we demonstrate that the present accepted approach is inconsistent with recognized drug disposition processes. However, this clearance relationship can be easily corrected using Kirchhoff's Laws. The purpose of this review is to demonstrate that Kirchhoff's Laws, which define how to approach rate processes that occur in parallel versus processes that occur in series, can be applicable to pharmacology in addition to the over 160-year recognition of their use in physical sciences. We anticipate that the application to clearance will be only the first of many such pharmacological analyses.

Keywords

Clearance; Intrinsic clearance; Kirchhoff's Laws; Liver; Kidney

1. Introduction

Mathematical models of drug clearance rates in the body have traditionally been derived based on particular dynamic mechanisms, for example the notion of a well-stirred model (WSM). Here, we review a more general derivation, independent of mechanistic details,

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using Kirchhoff's Laws combined with knowledge of which flow processes are in series vs. parallel. Clearance (CL) is the most important pharmacokinetic parameter as it defines the dosing rate for drugs in patients to achieve efficacy and minimize toxicity. At any i^{th} time-point, CL (volume/time) is defined as the rate of elimination (R_{elim}, mass/time) divided by the systemic exposure at that time-point (C_i, mass/volume) that is driving elimination (Benet et al., 2021) as given in Eq. 1

$$CL = \frac{R_{elim}}{C_i} \quad \text{(Eq. 1)}$$

There are many processes in the body contributing to drug clearance, although the primary sites for elimination are the kidney and liver. In the kidney, there are several renal elimination processes all influenced by the steady-state concentration input occurring independently of each other, whereas in the liver, there are several hepatic elimination processes occurring in sequence. The question arises: can clearance rates for each process be simply combined into net clearance rates CL_R and CL_H for the kidney and liver, respectively, without solving differential equations?

For decades, this question has been answered with specific mechanistic models, including primarily the so-called "well-stirred model" (Rowland et al.,1973; Wilkinson & Shand, 1975). However, conditions for the WSM have been deemed non-physiological - and yet, when researchers have proposed equations based on seemingly more physiologically-sound models, the WSM-derived equation continues to best match experimental data (Pang et al., 2019; Sodhi et al.,2020). A previously unconsidered conclusion is that the equations that follow from the WSM must be valid for reasons other than those provided by the WSM. Here we show that the presently employed CL_R equations under all conditions and CL_H equations for drugs where hepatic basolateral transporters are not clinically relevant may be easily derived based on Kirchhoff's Laws (as we define subsequently) independent of specific mechanistic models. Thus, the liver clearance data would be believed to fit the WSM, when in fact Kirchhoff's Laws give the same equation. However, when basolateral hepatic transporters are clinically relevant, the presently utilized mechanistic model requires an illogical conclusion as we detail subsequently. The correct relationship can be easily obtained following Kirchhoff's Laws. We believe that this is the first application of Kirchhoff's Laws to pharmacological processes but anticipate that many more uses will be identified in the future.

2. Application of Kirchhoff's Laws to Pharmacological Process

As pharmacologists and medical scientists may not be familiar with or do not recall the discussion, proof and application of Kirchhoff's Laws to physical and electrical processes, we provide at the end of this manuscript a Theoretical Background section as a reminder and guidance. In 1857 Gustav Kirchhoff published two papers, the first titled in English "On the Motion of Electricity in Conductors" (Kirchhoff, 1857a) and the second titled in English "On the Motion of Electricity in Wires" (Kirchhoff, 1857b). In the first paper

he demonstrated that when electrical resistors were in parallel, the total conductance (the inverse of resistance) was equal to the sum of the two conductances (Kirchhoff, 1857a), which has been subsequently designated as Kirchhoff's Current Law. In the second paper he demonstrated that when two resistors are in series, the inverse of the total conductance is equal to the sum of the inverse conductance for each resistor (Kirchhoff, 1857b), which has been subsequently designated as Kirchhoff's Voltage Law. The take home application of relevance here, based on the Theoretical Background, is that when two or more rate limiting processes are in parallel the total value of the measured outcome parameter is equal to the sum of those rate limiting processes. While when two or more rate limiting processes are in series the inverse of the total measured outcome parameter is equal to the sum of the inverse of those rate limiting parameters. Here we show these relationships for clearance as the measured outcome parameter when rate limiting processes are in parallel (Eq. 2) and in series (Eq. 3).

$$CL_{total} = CL_{rate\ limiting\ parallel\ process\ 1} + CL_{rate\ limiting\ parallel\ process\ 2} + \ldots \quad \text{(Eq. 2)}$$

$$\frac{1}{CL_{total}} = \frac{1}{CL_{rate\ limiting\ sequencial\ process\ 1}} + \frac{1}{CL_{rate\ limiting\ sequencial\ process\ 2}} + \ldots \quad \text{(Eq. 3)}$$

3. Application to Bodily Clearance Rates

3.1 Renal Clearance

In the kidney, there are three independent - i.e., parallel – renal clearance processes, all influenced by the steady-state concentration input. There is glomerular filtration (GF), in which the unbound fraction f_{uB} of drug molecules in the blood is filtered by the glomeruli at a rate of GFR , corresponding to a clearance rate of $CL_{GF} = f_{uB} \cdot GFR$. There is also secretion of the drug molecules by drug transporters into the urine through other parts of the kidney (i.e., proximal tubule) occurring at a clearance rate of CL_{sec} . Lastly, there is reabsorption of drug molecules back into the bloodstream, occurring at a clearance rate of $-CL_{reab}$, where CL_{reab} is a positive number, but it gets a minus sign because it corresponds to flow occurring in the opposite direction of the other flows, back into the bloodstream rather than out of it.

Applying Eq. 2 we immediately get:

$$CL_R = CL_{GF} + CL_{sec} + CL_{reab} = f_{uB} \cdot GFR + CL_{sec} + (-CL_{reab}) = f_{uB} \cdot GFR + CL_{\mathrm{sec}} - CL_{reab} \quad \text{(Eq. 4)}$$

We note that there is no net passive secretory clearance of drug in the kidney tubule following the glomerulus, since the free drug concentrations initially in the tubule and blood are equal but with fluid reabsorption (glomerular filtration rate in a healthy individual is ~120 ml/min but urine flow is only ~1 ml/min) drug concentrations in the tubule will rapidly

exceed blood concentrations so that CL_{reab} will be the combination of passive reabsorption and any potential active reabsorption. The concept that renal clearance process act in parallel and are additive has been well recognized as Eq. 4 has existed in the literature and in use for decades (Smith, 1950). In this review we just show that although not previously recognized as following Kirchhoff's laws, the correct equation results.

3.2 Hepatic Clearance

In the liver, there are several sequential clearance processes. First, the drug enters the liver at the rate of blood flow into the liver Q_H (hepatic blood flow in a healthy individual is ~1500 ml/min), which is itself the clearance rate CL_{ent} for this first step. There are then metabolic and biliary excretion processes occurring in parallel, with intrinsic rates CL_{met} and CL_{bil} , respectively, summing up to the total intrinsic rate CL_{int}. Utilizing Eq. 2, and with the recognition that these processes operate on the unbound fraction f_{uB} of drug molecules in the blood, the total rate for this elimination clearance step is $CL_{elim} = f_{uB} \cdot CL_{int} = f_{uB} \cdot (CL_{met} + C_{bil})$. If basolateral hepatocyte transporters are relevant, the pathway also includes a step with intrinsic clearance rate PS_{influx} due to transporters removing the unbound fraction f_{uB} from the bloodstream at a clearance rate of $CL_{influx} = f_{uB} \cdot PS_{influx}$, which can be modulated by PS_{efflux} in the opposite direction. PS_{efflux} is the intrinsic rate at which the unbound drug is returned to the bloodstream, resulting in $CL_{efflux} = f_{uB} \cdot PS_{efflux}$, which when compared to CL_{influx} has a minus sign due to its opposite direction. Forward and backward reversible steps must always be considered as parallel processes since it is not possible for the backward step to be the rate limiting process, a potential outcome for all in-series steps. Having enumerated all of the sequential steps, we simply add the inverse clearance rates, as instructed in Eq. 3, yielding:

$$\frac{1}{CL_H} = \frac{1}{CL_{ent}} + \frac{1}{CL_{elim}} + \frac{1}{CL_{influx} - CL_{efflux}} \quad \text{(Eq. 5)}$$

$$\frac{1}{CL_H} = \frac{1}{Q_H} + \frac{1}{f_{uB} \cdot CL_{int}} + \frac{1}{f_{uB} \cdot (PS_{influx} - PS_{efflux})}$$

Then

$$CL_H = \frac{Q_H \cdot f_{uB} \cdot CL_{int} \cdot (CL_{influx} - CL_{efflux})}{f_{uB} \cdot CL_{int} \cdot (CL_{influx} - CL_{efflux}) + Q_H \cdot (CL_{influx} - CL_{efflux}) + Q_H \cdot CL_{int}} \quad \text{(Eq. 6)}$$

If basolateral transporter processes are not relevant, Eq. 5 reverts to:

$$\frac{1}{CL_H} = \frac{1}{Q_H} + \frac{1}{f_{uB} \cdot CL_{int}} \quad \text{(Eq. 7)}$$

which becomes

$$CL_H = Q_H \cdot \frac{f_{uB} \cdot CL_{int}}{Q_H + f_{uB} \cdot CL_{int}}$$

(Eq. 8)

Again, as with Eq. 4, this equation has existed in the literature and in use for decades believing it to be the WSM. We believe this is the first publication showing how simple its derivation can be following Kirchhoff's Laws, without any assumptions related to hepatic drug disposition.

When basolateral transporter processes are relevant, hepatic blood flow effects are usually negligible, since the hepatic blood flow is much greater than the transporter clearances and Eq. 5 becomes

$$\frac{1}{CL_H} = \frac{1}{f_{uB} \cdot CL_{int}} + \frac{1}{f_{uB} \cdot (PS_{influx} - PS_{efflux})}$$

(Eq. 9)

which when solved for CL_H gives

$$CL_H = \frac{f_{uB} \cdot CL_{int} \cdot (PS_{influx} - PS_{efflux})}{CL_{int} + (PS_{influx} - PS_{efflux})}$$

(Eq. 10)

and when numerator and denominator are divided by CL_{int} yields

$$CL_H = \frac{f_{uB} \cdot (PS_{influx} - PS_{efflux})}{1 + \frac{(PS_{influx} - PS_{efflux})}{CL_{int}}}$$

(Eq. 11)

4. Discussion and Outlook

Using Kirchhoff's Laws, the renal and hepatic clearance equations may be easily calculated independent of any mechanistic model of organ elimination. These organ model-independent equations are consistent with the data in the literature both for hepatic and renal clearance measurements. Although investigators proposed and tested mechanistic models of hepatic organ elimination, all experimental evidence (when basolateral transporters are not clinically relevant) appears to only be consistent with Eq. 8 (Sodhi et al., 2020; Pang et al., 2019). This is consistent with the recognition that all published clearance values are arterial clearance numbers (Benet & Sodhi, 2022) and thus should be unaffected by the organ mechanistic model. At present physiologically based pharmacokinetic (PBPK) approaches often include different mechanistic models of hepatic organ elimination, such as the parallel tube or dispersion models, in trying to predict a clearance parameter that is independent of mechanistic models. The appropriate relationship is Eq. 8, which previously was only

believed to be consistent with the WSM but is now recognized to be the universal relationship independent of any mechanistic model of the organ.

However, as stated in the Introduction, the equations currently used to predict hepatic clearance when basolateral transporter effects are relevant are not consistent with Eq. 11. Rather the equation universally used in the literature (e.g., Sirianni & Pang, 1997; Webborn et al., 2007; Kusuhara & Sugiyama, 2009; Caminesh & Umehara, 2012; Barton et al., 2013; Patilea-Vrana and Unadkat, 2016) when hepatic blood flow is much greater than the transporter clearances is

$$CL_H = \frac{f_{uB} \cdot PS_{influx} \cdot CL_{int}}{CL_{int} + PS_{efflux}} \quad \text{(Eq. 12)}$$

From this equation, it is concluded that PS_{influx} may become the rate limiting step in hepatic elimination for substrates of hepatic uptake transporters such as the organic anion transporting polypeptides (OATPs) when PS_{efflux} is either zero or negligible compared to the irreversible elimination clearance, since then the CL_{int} values in the numerator and denominator of Eq. 12 will cancel. This is the same conclusion one would reach with Eq. 11 when $CL_{int} >> PS_{influx}$ (if PS_{efflux} is zero). Yet, in reality, the rate limiting step is ($PS_{influx} - PS_{efflux}$) as per Eq. 11. That is, the difference in the influx and efflux clearances is the rate limiting step with respect to hepatic basolateral transporters. Neither influx nor efflux alone will be rate limiting. Even when influx clearance is inhibited, it is the difference between influx and efflux that will be rate limiting. Thus, there is no need to assume efflux is negligible for transporter processes to be rate limiting. However, one must accept an illogical outcome from the widely used Eq. 12 approach. According to Eq. 8 if basolateral hepatic transporters are relevant to any extent, it is impossible for metabolic and/or biliary elimination to be the rate limiting step in hepatic elimination independent of the transporter clearances. This illogical predictive outcome disappears when Kirchhoff's Laws are used to derive clearance equations as in Eq. 11. Then, when CL_{int} is the slowest rate limiting step, this is the expected outcome from Eq. 11 independent of the values for the transporter clearances.

We have shown in this manuscript that physical relationships recognized for the past 160 years may be readily applied to a pharmacological rate process by considering whether the drivers of the process are in parallel or in series (or any combination of parallel and sequential drivers). There are many important rate processes that define pharmacological outcomes that are now derived in terms of differential equations that become operative at steady-state when the differential equations are set to zero. In the clearance analyses presented here we employed no differential equations, although in the Theoretical Background below we do assume linear force-flow and that these processes exhibit mass balance at a local equilibrium (the same assumptions required for differential equation derived processes). Thus, we believe that the presentation here will serve as a template for applying Kirchhoff's Laws to many other pharmacological and clinical outcomes.

5. Theoretical Background

5.1 Linear Force-Flow Relations

If we rearrange Eq. 1 ever-so-slightly, we get:

$$R_{elim} = CL \cdot C_i \tag{Eq. 1A}$$

For physicists and many other scientists, this equation may bring to mind similar-looking relationships: Fick's Law of Diffusion, drag force on falling objects, and where we focus now - Ohm's Law for Electric Current, among many others. These equations all share a basic form:

$$J = K \cdot f \tag{Eq. 13}$$

where J is some sort of current or flux, f is some driving force or impetus causing that flux, and K is a coefficient of proportionality determining the magnitude of the flux response to the input force. Note that K can be positive or negative, depending on the direction of the flux in response to the input. In Eq. 1A, we see that the rate of elimination, R_{elim}, serves as the current or flux, the input concentration C_i is the impetus driving the processes of elimination to occur, and thus the clearance rate CL is the constant of proportionality. In Ohm's Law, analogously, the electric current (I) serves as the flux, the voltage (V) is the driving force causing current flux, and in this case the conductance $\sigma = 1/R$ - which equals the inverse of the resistance - is the coefficient of proportionality:

$$V = I \cdot R \Rightarrow I = \sigma \cdot V \tag{Eq. 14}$$

5.2 Why Linear?

One might ask where an equation like Eq. 13 comes from in the first place? Why should a flux rate be directly proportional to the force driving it, as opposed to some other more complicated function? The reason we use equations of this form so often is two-fold: the first is simply that it works, i.e., it has been matched very successfully to a plethora of diverse situations. The second reason comes from some quick calculus. Let us say that the flux or current J is some more complicated function $g(f)$ of the driving force f; what can we say immediately about this function? First, we expect the flux rate to flip signs when the driving force flips signs; if we push something to the right and it moves to the right, then we expect it to move to the left when we move it to the left. This means the function $g(f)$ must be odd in f, i.e., $g(-f) = -g(f)$. From this, we immediately get that $g(0) = g(-0) = -g(0)$, therefore $g(0) = 0$. This is a good outcome, this is what we expect, as there will be no flux without any input.

Next, we perform a Taylor expansion around $f = 0$; this means we are assuming that f small in some sense, relative to some relevant scale. The first few terms are:

$$J = g(f) + g'(0) \cdot f + 1/2g''(0) \cdot f^2 + O\left(f^3\right)$$

(Eq. 15)

But we said that $g(f)$ is odd, which means not only is $g(0) = 0$, but also any even derivative of $g(f)$ is equal to zero, so there are no even powers of f in the Taylor expansion. That leaves us with:

$$J = g'(0) \cdot f + O\left(f^3\right)$$

(Eq. 16)

We can compare Eq. 15 with Eq. 13 and identify the coefficient of proportionality as $K = g'(0)$. We see now that Eq. 13 is indeed very general, provided the driving force is not too large. It is important to always remember that we could have nonlinearities whenever a driving force gets too large, even though the linear approximation has been so experimentally successful.

There are two other small notes that will not be discussed in detail here but are nevertheless important to remember: (a) J really represents an average flux. The flux at any given moment can fluctuate above and below this average value, depending on the system; it is only the average J that satisfies Eq. 13 and (b) Eq. 13 assumes the equality of ratios between fluxes and forces in systems out of equilibrium, but where a notion of local equilibrium exists, i.e., when the input driving force has been held constant long enough that the macroscopic parameters of the system settle into constant values themselves. When the driving force changes, there are generally transient fluxes as the system settles into a new local equilibrium. Both the assumptions of notes a) and b) are also required for differential equation derived processes.

Having acknowledged the above, we will simply refer to J as the flux rate, where the driving force has been constant for a sufficient time, and thus the system is in a local equilibrium.

5.3 Parallel and Series

Now we may ask how to combine fluxes for different processes into net flux. We will do so in perfect analogy with the determination of effective resistance (or effective conductance) in electric circuits containing multiple resistors, derivations that many high school and college freshmen physics students see every year. These derivations employ Kirchhoff's Laws, which, in the language we have introduced here, are quite simple.

Kirchhoff's Current Law (KCL) states that, if multiple branches of current or flux meet at a point, the net flux going into the point must equal the net flux exiting the point, which he used to refer to electric currents and nodes in circuits. We use this to study a parallel setup, in which two independent processes can be considered two branches of flux, whereby

the flux through each branch must add up to the net flux, according to KCL. That means $J = J_1 + J_2$, where the subscripts refers to the number of different processes being evaluated. We then plug in Eq. 15 noting that the driving force acting on each branch is the same, i.e., $f_1 = f_2 = f$, yielding:

$$K \cdot f = J = J_1 + J_2 = K_1 \cdot f_1 + K_2 \cdot f_2 = K_1 \cdot f + K_2 \cdot f$$

Therefore

$$K = K_1 + K_2 \qquad \text{(Eq. 17)}$$

So, we see that coefficient of proportionality for parallel processes simply add, and that this is a very general result.

Similarly, Kirchhoff's Voltage Law (KVL) states that, if multiple processes occur in sequence, the driving forces for each process add up to the total driving force; Kirchhoff actually used this to describe voltages adding up to zero in any closed loop in an electric circuit, but more generally it can be taken to mean driving forces adding up for processes in sequence; in our terminology, this means $f = f_1 + f_2$. We can plug this into a rearranged Eq. 13, $f = J/K$, noting that, since the processes all occur along the same pathway, the flux rate through each of them must be the same, i.e., $J = J_1 = J_2$, yielding:

$$\frac{J}{K} = f = f_1 + f_2 = \frac{J_1}{K_1} + \frac{J_2}{K_2} = \frac{J}{K_1} + \frac{J}{K_2} = J \cdot \left(\frac{1}{K_1} + \frac{1}{K_2}\right)$$

Therefore:

$$\frac{1}{K} = \frac{1}{K_1} + \frac{1}{K_2} \quad \text{and} \quad K = \frac{K_1 \cdot K_2}{K_1 + K_2} \qquad \text{(Eq. 18)}$$

So, we see that coefficients of proportionality for series processes add in inverse, and that this is a very general result. In the second part of Eq. 15, we simply rearranged this result into a different, commonly used form.

As we prefaced, these results, Eqs. 13 and 14, bear great resemblance to, and are in fact more general cases of, the laws for combining resistances in electric circuits, though they are switched around since these formulas apply to the inverse resistances, known as conductances, rather than to the resistances themselves. The same deep underlying principle that justifies application of Kirchhoff's Laws to electrical currents also justifies application to the situation addressed here, namely of drug molecules flowing across membranes and organ barriers. In particular, Kirchhoff's laws apply to any flow of conserved particles/ units/ agents that are driven by a potential function. In electrical flows, those particles are electrons or ions. They are conserved: within a flow, the particles are neither created nor destroyed.

And they are driven by an electrostatic potential energy. The same conservation laws and forces apply to drugs and other pharmacological molecules. They are conserved and subject to chemical potentials (Dill and Bromberg, 2010).

Having derived these general results for combining coefficients of proportionality, we return to Section 3 of the manuscript where they can be quickly and easily applied to clearance rates from various processes in the liver and kidney.

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Abbreviations:

C_i	systemic concentration at the ith time point
$\boldsymbol{CL}$	clearance
CL_{bil}	intrinsic biliary clearance
CL_{elim}	elimination clearance
CL_{ent}	entering clearance
CL_H	hepatic clearance
CL_{int}	intrinsic clearance
CL_{met}	intrinsic metabolic clearance
CL_R	renal clearance
CL_{reab}	reabsorption clearance
CL_{sec}	secretion clearance
f	driving force causing flux
f_{uB}	fraction unbound in blood
$\boldsymbol{GF}$	glomerular filtration
$\boldsymbol{GFR}$	glomerular filtration rate
$\boldsymbol{I}$	current
$\boldsymbol{J}$	flux

K	coefficient of proportionality
KCL	Kirchhoff's Current Law
KVL	Kirchhoff's Voltage Law
OATP	organic anion transporting polypeptide
PS	intrinsic transporter clearance either influx or efflux
Q_H	hepatic blood flow
R	resistance
R_{elim}	rate of elimination
σ	conductance
V	voltage
WSM	well-stirred model

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