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A MATHEMATICAL MODEL FOR ANTIBIOTIC CONTROL OF BACTERIA IN PERITONEAL DIALYSIS ASSOCIATED PERITONITIS

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Abstract. A study of the process of pharmacokinetics-pharmacodynamics (PKPD) of antibiotics and their interaction with bacteria during peritoneal dialysis associated peritonitis (PDAP) is presented. We propose a mathematical model describing the evolution of bacteria population in the presence of antibiotics for different peritoneal dialysis regimens. Using the model along with experimental data, clinical parameters, and physiological values, we compute variations in PD fluid distributions, drug concentrations, and number of bacteria in peritoneal and extra-peritoneal cavities. Scheduling algorithms for the PD exchanges that minimize bacteria count are investigated.

1. **Introduction.** There are two types of renal replacement therapy: hemodialysis and peritoneal dialysis (PD). One of the major concerns of peritoneal dialysis is peritonitis or inflammation of the peritoneal membrane (peritoneum) due to bacterial infection. In PD the peritoneal membrane, a natural lining of the abdomen, is used as a filter to eliminate the body toxins. A periodic exchange of water and solutes across the peritoneum replaces the filtering function of the kidney. By means of a catheter that is surgically inserted into the patient abdomen, a hypertonic solution (dialysate) containing dextrose or sugar fills the abdominal cavity. During dwelling of the dialysate in the peritoneal cavity, the waste products diffuse from the blood capillaries covering the peritoneal tissue and across the peritoneum into the peritoneal fluid. There is an increasing interest in peritoneal dialysis associated peritonitis (PDAP) due to the recent emergence of a growing number of antibiotic resistant strains of bacteria [6],[2]. Comparative studies on the killing of bacteria by specific antibiotics acting on contaminated PD fluid in vitro have been already

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discussed in the literature, see e.g. [1],[4],[10]-[13]. Some clinical studies with different antibiotics for treatment of peritonitis associated with peritoneal dialysis have been discussed on the basis of statistical analysis in [7] and [9]. In this paper we investigate the effect of antibiotics (such as trovafloxacin) on bacteria population living in the peritoneal cavity fluid during PD treatment in vivo. We propose a mathematical model to evaluate the fluid levels, antibiotic concentrations, and the number of bacteria in peritoneal and extra-peritoneal cavities (PC and EPC). One of the main problems of mathematical modeling of a biological system in vivo is that it is very hard to take direct measurement of any physical quantity. From our model we can compute a number of dynamical characteristics of the system, such as drug concentration in different compartments, flow rates, evaluate bacteria population size, and volumes of fluid distribution, for any time interval. Thus, our model can be used to evaluate the changes in bacterial population for different treatment regimens (exchange schedules). These changes can be analyzed for multiple cycles repeated over long periods of time, and provide valuable information about the system, that otherwise would not be easily accessible. Thus, the main goals of this work are to develop a better understanding of the population dynamics of bacteria living in the peritoneal cavities during PD therapy, and thereby provide guidance to clinicians for treatment of peritonitis.

A first attempt to optimize PD treatment with antibiotics using a mathematical model was presented in [5]. A Monte Carlo approach was employed for two different types of treatment regimens: continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). The Monte Carlo implementation was based on the variability of patient physiology. The model outcomes were the percentage of time when the anti-microbial concentration was at least five times the MIC (minimal inhibitory concentration) and the mean of AUC/MIC in the extra-peritoneal cavity (AUC is the area under the concentration curve). Bacteria counts were not part of this model. The present construction is an extension and an improved version of the model in [5]. Here, we include the additional effect of bacteria initially infecting the peritoneal cavity through a catheter inserted in PC, then spreading ultimately into EPC. Bacteria are assumed to be carried into the extra-peritoneal area by the portion of extra-cellular water that is retained in the extra-peritoneal compartment. Our model focuses on the dynamics of the bacterial population in fluid phase in both PC and EPC. Unlike [5] we take into account the process of filling and draining of the dialysate in and out of the peritoneal cavity, considering that a number of bacteria will be carried by the PD fluid flow and assuming that the flow rates into and from the peritoneal cavity are no longer constants but are functions of time. In addition we consider that the portion of water retained in the cells of extra-peritoneal tissue is not negligible contrary to the assumption of the previous model.

2. **Mathematical model.** We investigate the dynamics of peritoneal fluid and bacterial population by considering the transport through the peritoneal membrane, and the PKPD of antimicrobial agent administered during PD treatment. The model is temporal and unlike [5] includes three compartments: (i) the dialysate bag, (ii) the PC and (iii) the EPC. The compartments are depicted in Figure 1. We study the evolution of the bacterial population in PC and EPC depending on two major factors: the antibiotics action and the dynamics of the peritoneal fluid distribution in both cavities. Upon entering blood circulation most drugs bind

rapidly to protein molecules (blood components) and their protein-bound fraction stays inactive. The efficacy of a drug is measured by the action of its unbound quantity [12]. Free (unbound) drug can easily traverse cell membranes unlike its protein bound portion. In this paper we study the changes of the antimicrobial concentration in time, and changes in bacteria count in each compartment. The model is based on balance equations between the three compartments. We set up and solve the system of seven constitutive equations for seven non-negative functions of time:

- volume of distribution of fluid in the PC, $V_p(t)$ (ml)
- volume of distribution of fluid in the EPC, $V_{ep}(t)$ (ml)
- amount of bound drug in the EPC, $D_{epb}(t)$ (mg)
- amount of free drug in the EPC, $D_{epf}(t)$ (mg)
- amount of antimicrobial agent in the PC, $D_p(t)$ (mg)
- number of bacteria in the PC, $X_p(t)$
- number of bacteria in the EPC, $X_{ep}(t)$.

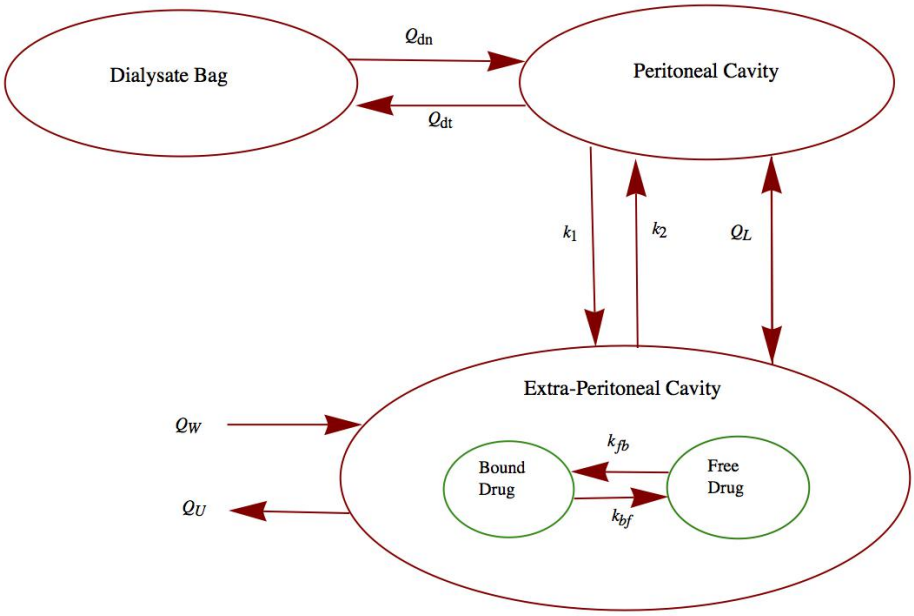

FIGURE 1. Diagram of PD Model

Since the protein binding of drug molecules in the PC is believed to be of less clinical importance, we consider only binding in the EPC. We focus our interest on evaluating different antibiotic treatment regimens. A typical continuous ambulatory peritoneal dialysis regimen includes four daily short cycles of 4 hours each and one long cycle of eight hours at night. The same cycles are repeated every day. We assume that a dose of antimicrobial agent is administered to a patient suffering from peritonitis (adult male 70 kg) at each cycle exchange. An antibiotic is added

to the dialysate, which is then infused into the PC. After a dwelling period in PC, the infused fluid is then drained out of PC. We assume that the bacteria are coming from the catheter and subsequently are infecting the PC and EPC. These bacteria are believed to be in planktonic form (fluid phase) in all compartments. We assume that despite host-defense action, the population of bacteria increases with time and bacteria are carried into EPC with the peritoneal dialysis fluid (PDF). We study the case where bacteria in EPC are being transported by the portion of extra-cellular water retained in extra-peritoneal tissue.

Let us describe the model equations and assumptions. Bacteria population is modeled by a logistic growth curve. The killing effects of the antimicrobial drugs are assumed to follow the same type of relations as in [12]. A review of the different PKPD models that are presently available in the literature is given in [10]. The pharmacokinetics are based on unpublished models by P.S. Crooke and J.R. Hotchkiss. These models were obtained using nonlinear regression analysis for different combinations of antibiotics and bacteria measured from past experimental results. We study the time evolution of the number of bacteria living in both cavities over several cyclic exchanges of the PDF. Each cycle has three phases: (1) the infusion period of the dialysate into PC, (2) the dwelling period of the PDF in the PC and (3) the drainage period of the fluid containing the biological wastes, excess salt, and water out of PC. We examine ways to optimize bacterial clearance. It is assumed that a non-negligible amount of microorganisms (bacteria and macrophages as well) are being flushed out during drainage period at each exchange. In our analysis, the residual bacteria in the PC at the end of a cycle become the initial condition for the next cycle. Reaching an adequate balance between the increasing number of bacteria and the killing action of antimicrobial drugs is an effective way to eradicate the infection and minimize at the same time the negative effects of antibiotics on the patient. We model the killing effect of antibiotic (Trovafloxacin) on the microbial population (Bacteroides Fragilis) living in both cavities, neglecting the immune system response, and assuming only that part of the bacterial population is being flushed away at each drainage exchange. It is assumed that the rate of dialysate flow entering (or exiting) the PC stays constant and is independent of the cycle. The lymphatic flow is unidirectional and of constant rate. However the ultrafiltration is bidirectional and its rate varies in time during any cycle according to a prescribed function of time. The notations, values and definitions of the model parameters and variables partially taken from [3], [5], [12], [13], are summarized in Table 1.

The first two equations are balance equations of fluids in both compartments: PC and EPC:

$$\frac{dV_p}{dt} = Q_D - Q_L + (1-\alpha_0)Q_W, \tag{1}$$

where

$$\begin{aligned} Q_D(t) &= Q_{dn}(t) - Q_{dt}(t), \\ Q_L(t) &= Q_l + Q_f(t), \\ Q_W(t) &= Q_0 + Q_c(t), \end{aligned}$$

Q_l is the lymphatic flow rate (assumed constant), and $Q_f(t)$ is the ultrafiltration flow rate function which is assumed to take the form:

$$Q_f(t) = q_{fm}\left(e^{-4t/T} - t/T\right)U(t-T_1),$$

see Table 1 for information on all other parameters. Here $U(.)$ is the unit-step function.

The rate of change of the volume of fluid in PC $V_p(t)$ is determined by the flow of dialysate $Q_D(t)$ in and out of the dialysate bag, the net lymphatic/ultrafiltration rate $Q_L(t)$ between the PC and EPC (ultrafiltration is happening at cell membrane level when solute molecules are filtered in and out of blood capillaries of the EPC tissue), and the net flow of water $Q_W(t)$ into the peritoneal cavity through tissues (Figure 1). Note that the net flow rate $Q_W(t)$ is the sum of the flow rate of water ingested orally by the body Q_0 and the intra-cellular flow rate $Q_c(t)$. We assume that water is filtered into the PC except for a small fraction α_0 that is retained in the extra-peritoneal tissue. In addition, we assume that the flow rate of water crossing the cell boundaries is higher during the first mid-cycle, and the ultra-filtration rate $Q_L(t)$ is zero during the infusion period of the dialysate into the PC.

For the volume of fluid in EPC, $V_{ep}(t)$ we obtain a similar equation :

$$\frac{dV_{ep}}{dt} = \alpha_0 Q_W + Q_L - Q_U. \tag{2}$$

The volume of the EPC fluid V_{ep} depends on the rate of renal elimination $Q_U(t)$, a portion of the fluid that flows from EPC to the kidney (see Figure 1).

The next three equations represent the mass transfer of anti-microbial drug in PC and EPC. As noted above in PC the drug is considered unbounded, and therefore the mass of antibiotic $D_p(t)$ in PC is the only essential characteristic of the drug in peritoneal cavity. However in EPC at the cellular level the drug can be in both protein-bound D_{epb} and unbound D_{epf} states, and there is a reversible equilibrium between these two states [12].

The rate of change of the amount of bound drug present in the EPC D_{epb} is modeled by the mass balance equation:

$$\frac{dD_{epb}}{dt} = k_{fb} D_{epf} - k_{bf} D_{epb} - \frac{D_{epb}}{\alpha_0 V_{ep}} Q_U. \tag{3}$$

In (3) the rate of change of the amount of bound drug $\frac{dD_{epb}}{dt}$ is determined by the rate of production of bound drug from free drug $k_{fb}D_{epf}$, the rate of production of free drug from bound drug $k_{bf}D_{epb}$, and the rate of renal elimination from the cavity Q_U. The parameters k_{bf} and k_{fb} are constant transfer rates between bound drug and free drug states, respectively. The last term is the rate of drug elimination. As noted above α_0 is a fraction of water (or extra-cellular fluid) that is retained in the extra-peritoneal tissues, or more precisely, it is a fraction of the fluid that can circulate freely, therefore, contributing to renal elimination. $\frac{D_{epb}}{\alpha_0 V_{ep}}$ is the density of drug in EPC, and Q_U is the rate of flow out of EPC into the kidney(s). Similarly, the rate of change of the amount of free drug in the EPC D_{epf} obeys the equation:

$$\frac{dD_{epf}}{dt} = k_1 D_p - k_2 D_{epf} + k_{bf} D_{epb} - k_{fb} D_{epf} - \frac{D_{epf}}{\alpha_0 V_{ep}} Q_U. \tag{4}$$

The first term $k_1 D_p$ is the mass rate of antimicrobial drug being filtered into the EPC from PC through the peritoneal membrane, the second term $k_2 D_{epf}$ is the amount (rate) of drug being reabsorbed into the PC, the third and fourth terms give the amount (rate) of free drug produced in the EPC (amount of bound drug becoming free minus amount of free drug becoming bound), and the last term is

the amount (rate) of free drug lost through renal elimination. The constants k_1 and k_2 are mass transfer coefficients (rates) related to diffusion and convection between cavities, and are considered constants (see Table 1).

The rate of change of the antimicrobial agent present in the PC is modeled by the following differential equation:

$$\frac{dD_p}{dt} = \frac{D_{bag}}{V_{bag}} Q_{dn} + k_2 D_{epf} - k_1 D_p - (Q_{dt} + k_D Q_L) \frac{D_p}{V_p}. \tag{5}$$

In (5) the rate of change of the mass of drug D_p is determined by the in-flow rate from the dialysate bag Q_{dn} (first term), the amount of free drug being filtered back into the peritoneal cavity from EPC through diffusion or convection (second term), and the amount of drug going from PC to EPC (third term), which is absorbed by the peritoneum. The last term consists of two parts: the first part is determined by the drug out-flow rate into the dialysate bag Q_{dt} and the second part is the amount of drug going into the PC due to the net lymphatic/ultrafiltration rate.

We now consider the bacteria population in both peritoneal cavities. The dynamics of the bacteria population in the PC is governed by the following differential equation:

$$\begin{aligned} \frac{dX_p}{dt} =& \mu_1 \left(1 - \frac{X_p}{X_{M_1}}\right) X_p - \frac{\epsilon_1 D_p / D_{pm}}{1 + (C_{50} e^{-\alpha t}/C_0)^{\gamma_1}} X_p - \left(\frac{s_D Q_{dt}}{V_p} + \frac{s_L Q_{L_1}}{V_p}\right) X_p \\ &+ \frac{s_L Q_{f_2} X_{ep}}{\alpha_0 V_{ep}}. \end{aligned} \tag{6}$$

In (6) the time rate of change in the amount of bacteria $X_p(t)$ living in the PC is determined by four terms; see [8] and [13] for details. The first two terms describe the growth and death rates of bacteria respectively, while the last two terms represent the transport of bacteria in and out of PC. The logistic bacterial growth is measured by the coefficient rate μ_1 and the maximum population size X_{M_1}. The second term corresponds to the antibiotic killing rate, where ϵ_1 is the killing coefficient (see Table 1), and is proportional to the amount of drug $D_p(t)$ and the number of bacteria $X_p(t)$ in PC. The coefficients are defined from the profile of antibiotics serum levels [8] where C_0 represents the initial concentration of drug in serum and C_{50} is the concentration needed to produce a 50% killing rate of bacteria in serum (Table 1). The number of bacteria being transported out of the PC is calculated in the third term depends on the lymphatic flow Q_l, the ultrafiltration flow Q_{f_1} and dialysate flow Q_{dt}. Note that the lymphatic flow rate Q_l is constant unidirectional from PC to EPC, however the ultrafiltration rate $Q_f(t) = Q_{f_1}(t) - Q_{f_2}(t)$ is bidirectional and has a positive and a negative part. The positive part denoted by $Q_{f_1}(t)$ is used for the direction from PC to EPC in the third term of equation (6), while $Q_{f_2}(t)$ is used for the reverse motion from PC to EPC and is expressed in the last term. We introduce the notation $Q_{L_1} = Q_l + Q_{f_1}$ to represent the unidirectional lymphatic/ultrafiltration flow rate from PC to EPC. The constants s_D and s_L are transport coefficients associated with dialysate and lymphatic/ultrafiltration flow rates, respectively (see Table 1). The variations of the number of bacteria in the EPC is governed by a similar equation:

$$\begin{aligned}\frac{dX_{ep}}{dt} =&\mu_2\left(1-\frac{X_{ep}}{X_{M_2}}\right)X_{ep}-\frac{\epsilon_2 D_{epf}/D_{epm}}{1+(C_{50}e^{-\alpha t}/C_0)^{\gamma_2}}X_{ep}\\ &-\left(\frac{s_L Q_{f_2}}{\alpha_0 V_{ep}}+\frac{s_U Q_U}{\alpha_0 V_{ep}}\right)X_{ep}+\frac{s_L Q_{L_1}}{V_p}X_p.\end{aligned} \tag{7}$$

Compared to (6), equation (7) has an additional term with renal elimination rate Q_U, and s_U denotes the urine output transport coefficient.

In order to simplify the form of our system (1) - (7) we introduce the following notations:

$$Q_{\alpha_1}(t) = (1-\alpha_0)Q_W(t) - Q_l,$$

$$Q_{\alpha_2}(t) = \alpha_0 Q_W(t) - Q_U(t) + Q_l.$$

The equations for $V_p(t)$ and $V_{ep}(t)$ become:

$$\frac{dV_p}{dt} = Q_D(t) + Q_{\alpha_1}(t) - Q_f(t), \tag{8}$$

$$\frac{dV_{ep}}{dt} = Q_{\alpha_2}(t) + Q_f(t), \tag{9}$$

where

$$\begin{aligned}Q_D(t) &= Q_{dn}(t) - Q_{dt}(t),\\ Q_{dn}(t) &= \frac{V_{bag}}{T_1}(1-U(t-T_1)),\\ Q_{dt}(t) &= \frac{V_{bag}+V_{res}}{T_2}U(t-(T-T_2)).\end{aligned}$$

Therefore in one cycle of period T of filling time T_1 and drainage time T_2 , we have:

$$Q_D(t) = \begin{cases} V_{bag}/T_1, & t < T_1\\ 0, & T_1 \le t < T-T_2\\ -(V_{bag}+V_{res})/T_2, & T-T_2 \le t < T.\end{cases}$$

A similar calculation yields: $Q_U(t) = q_{u_{min}}(1-U(t-T_m)) + q_{u_{max}}U(t-T_m)$, where $q_{u_{min}}$ and $q_{u_{max}}$ are the minimum and maximum values of Q_U respectively. T_m is the half-time period (see Table 1). We also define:

$$Q_W(t) = Q_0 + Q_c(t) = Q_0 + (q_{cn}-q_{ct})((1-U(t-T_m)) - U(t-T_m)).$$

Let us assign the initial conditions for compartment volumes:

$$V_p(t_0) = V_{pres}, \qquad V_{ep}(t_0) = V_{epres},$$

where V_{pres} and V_{epres} represent the respective residual volumes of fluid of distribution from the PC and the EPC that are equal to volume outcomes at the end of previous cycle. We now construct a sequence of fill-drain cycles. During the i-th cycle of period $T(i) = t_0(i+1) - t_0(i)$, upon integration of the differential equations (8)-(9) over the time interval $[t_0(i), t]$, and omitting the index i we obtain the

volumes:

$$V_p(t) = V_{pres} + \int_{t_0}^{t} [Q_D(\delta) + Q_{\alpha_1}(\delta) - Q_f(\delta)]d\delta, \tag{10}$$

$$V_{ep}(t) = V_{epres} + \int_{t_0}^{t} [Q_{\alpha_2}(\delta) + Q_f(\delta)]d\delta. \tag{11}$$

Solutions for $V_p(t)$ and $V_{ep}(t)$ in terms of all model parameters are long and will not be given here. The equations (3)-(5) are written on the form:

$$\frac{dD_{epb}}{dt} = \left(-\frac{Q_U(t)}{\alpha_0 V_{ep}(t)} - k_{bf}\right) D_{epb}(t) + k_{fb} D_{epf}(t), \tag{12}$$

$$\frac{dD_{epf}}{dt} = k_{bf} D_{epb}(t) - \left(k_{fb} + k_2 + \frac{Q_U(t)}{\alpha_0 V_{ep}(t)}\right) D_{epf}(t) + k_1 D_p(t), \tag{13}$$

$$\frac{dD_p}{dt} = k_2 D_{epf}(t) - \left(k_1 + \frac{Q_{dt}(t) + k_D Q_L(t)}{V_p(t)}\right) D_p(t) + \frac{D_{bag}}{V_{bag}} Q_{dn}(t). \tag{14}$$

The system of differential equations (12)-(14) can be independently solved for $D_{epb}(t)$, $D_{epf}(t)$ and $D_p(t)$ by writing it in matrix form:

$$\frac{dY_p}{dt} = M(t)Y_p(t) + F(t), \tag{15}$$

where $Y_p(t)$ and $F(t)$ are column vectors of the form:

$$Y_p(t) = (D_{epb}(t), D_{epf}(t), D_p(t)),$$
$$F(t) = \left(0, 0, \frac{D_{bag}}{V_{bag}} Q_{dn}(t)\right),$$

$M(t)$ is the matrix-valued function

$$\begin{pmatrix} m_1(t) & k_{fb} & 0 \\ k_{bf} & m_2(t) & k_1 \\ 0 & k_2 & m_3(t) \end{pmatrix}$$

and

$$m_1(t) = -\frac{Q_U(t)}{\alpha_0 V_{ep}(t)} - k_{bf},$$
$$m_2(t) = -\frac{Q_U(t)}{\alpha_0 V_{ep}(t)} - k_{fb} - k_2,$$
$$m_3(t) = \frac{-k_D Q_L(t) - Q_{dt}(t)}{V_p(t)} - k_1.$$

The drug concentrations in PC and EPC denoted by $C_p(t)$ and $C_{epf}(t)$ respectively, can be easily derived from the formulas:

$$C_p(t) = \frac{D_p(t)}{V_p(t)}$$
$$C_{epf}(t) = \frac{D_{epf}(t)}{\alpha_0 V_{ep}(t)}.$$

Furthermore, differential equations (6)-(7) are reduced to:

$$\frac{dX_p}{dt} = \mu_1 \left(1 - \frac{X_p}{X_{M_1}}\right) X_p - A_1(t)X_p + B_1(t)X_{ep}, \tag{16}$$

$$\frac{dX_{ep}}{dt} = \mu_2 \left(1 - \frac{X_{ep}}{X_{M_2}}\right) X_{ep} - A_2(t)X_{ep} + B_2(t)X_p, \tag{17}$$

where we have set:

$$A_1(t) = \frac{\epsilon_1}{1 + \left(\frac{C_{50}}{C_0 e^{\alpha t}}\right)^{\gamma_1}} \frac{D_p(t)}{D_m} + \left(\frac{s_D Q_{dt}(t)}{V_p(t)} + \frac{s_L Q_{L_1}(t)}{V_p(t)}\right) \tag{18}$$

$$A_2(t) = \frac{\epsilon_2}{1 + \left(\frac{C_{50}}{C_0 e^{\alpha t}}\right)^{\gamma_2}} \frac{D_{epf}(t)}{D_{epm}} + \left(\frac{s_L Q_{f_2}(t)}{\alpha_0 V_{ep}(t)} + \frac{s_U Q_U(t)}{\alpha_0 V_{ep}(t)}\right) \tag{19}$$

$$B_1(t) = \frac{s_L Q_{f_2}(t)}{\alpha_0 V_{ep}(t)} \tag{20}$$

$$B_2(t) = \frac{s_L Q_{L_1}(t)}{V_p(t)}. \tag{21}$$

Although we cannot find analytical solution of the system (1)-(7) in general case the numerical solutions can be found using Mathematica. The results are summarized and discussed in the next two paragraphs.

3. **Results.** The simulations of the model have four perspectives: (i) calculations of $V_p(t)$, $V_{ep}(t)$, $C_p(t)$, $C_{epf}(t)$, $D_{epb}(t)$, $D_{epf}(t)$, $D_p(t)$, $X_p(t)$, $X_{ep}(t)$ over one 4-hour cycle; (ii) simulations over a one-day period using the schedule (4,4,4,4,8); (iii) simulations with permutations of (4,4,4,4,8); and (iv) simulations over a one-week period with different exchange strategies e.g., (8,8,8).

We first examine the dynamics of the model for clinical relevant values of the model parameters over one exchange cycle of length 4 hours (240 minutes). We study the evolution of the bacterial population assuming that the initial infection in PC is bacterial and no infection is present in the EPC. The computations are made considering the following first initial conditions: $D_p(0) = D_{epb}(0) = D_{epf}(0) = 0$, $V_p(0) = 50$ ml, $V_{ep}(0) = 31000$ ml, $X_p(0) = 10^6$ and $X_{ep}(0) = 10^{-4}$. Figure 2 shows the results of these simulations. We first observe that the volumes, concentrations and drug amounts from both cavities are represented by piecewise functions of time corresponding to three phases: filling, dwelling and drainage. We also notice that all variations during dwelling period are negligible. Therefore there are no significant changes in the model variables over time during dwelling of one exchange cycle. We notice that bacteria populations in both compartments increase fast and reach a plateau of relatively high values if we compare with the bacterial burden of 10^6 CFU/ml generally observed in PDAP [4].

Secondly, we examine the dynamics over five consecutive cycles using the sequence (4,4,4,4,8) for one-day treatment. We investigate the effect of the antimicrobial agent for a dose of 250 mg of trova given at each cycle exchange of CAPD treatment. The plots of the key outcome variables are given in Figure 3. We observe an increase in drug amounts and concentrations and a decrease in number of bacteria in both compartments. Thirdly, we consider permutations of the (4,4,4,4,8) schedule over a 24-hour period:

- Case 1. T=(8,4,4,4,4)
- Case 2. T=(4,8,4,4,4)

- Case 3. T=(4,4,8,4,4)
- Case 4. T=(4,4,4,8,4)
- Case 5. T=(4,4,4,4,8).

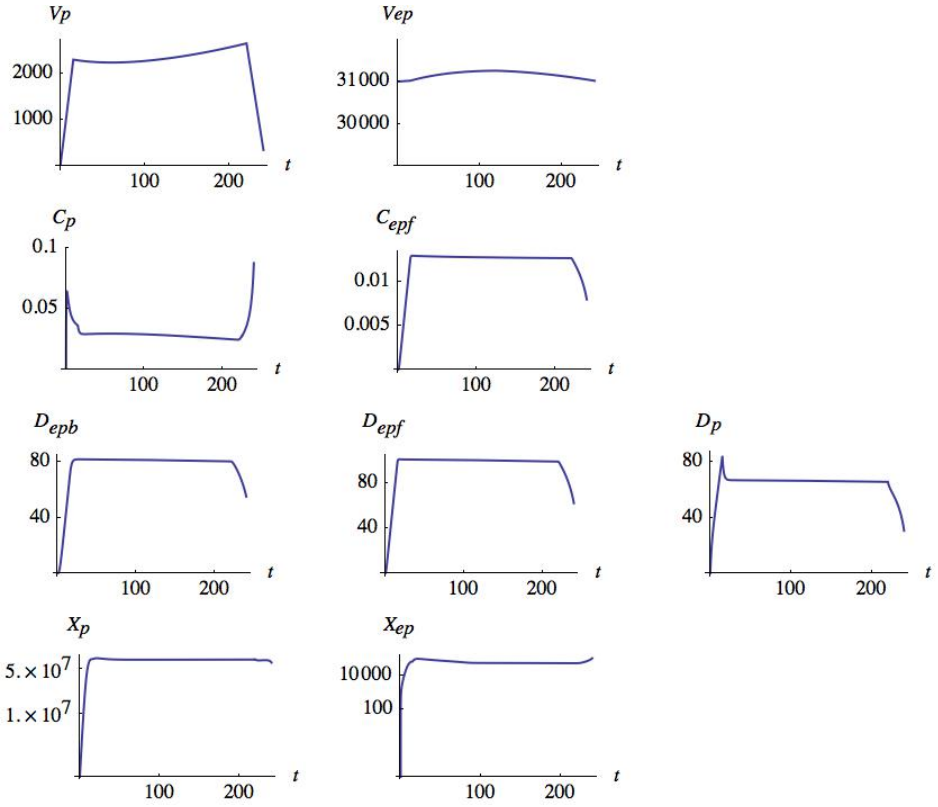

FIGURE 2. Plots of Volume of fluid distribution, drug concentrations, bound and free drug amounts, and bacteria counts in PC and EPC over one 4-hour cycle.

We want to see if the position of the 8-hour cycle has an effect on the bacteria population. For each cycle, 250 mg of antibiotics is administered while all other model parameters remain constant. Table 2 shows the results of the total number of bacteria from both cavities. The smallest number of bacteria occurs in Case 5 where the sequence of exchanges ends with the long cycle (which is the most natural CAD schedule when the last filling occurs while the patient is sleeping). This calculation assumes that we use the same model parameters and the same amount of antimicrobial prescribed at each exchange. Since the simulations are performed for the same number of cycles over a 24-hour period, the daily amount of drug given to the patient remains constant. Therefore, the antibiotic level does not vary during these different modes of treatment. We conclude that for the same amount of antibiotic a one-day of treatment is optimal in Case 5 when the long cycle is scheduled at the end of the day and preceded by four short cycles.

Lastly, we repeat the simulations for all possible combinations of cycle exchanges over 24 hours for a minimum number of 3 exchanges and a maximum number of

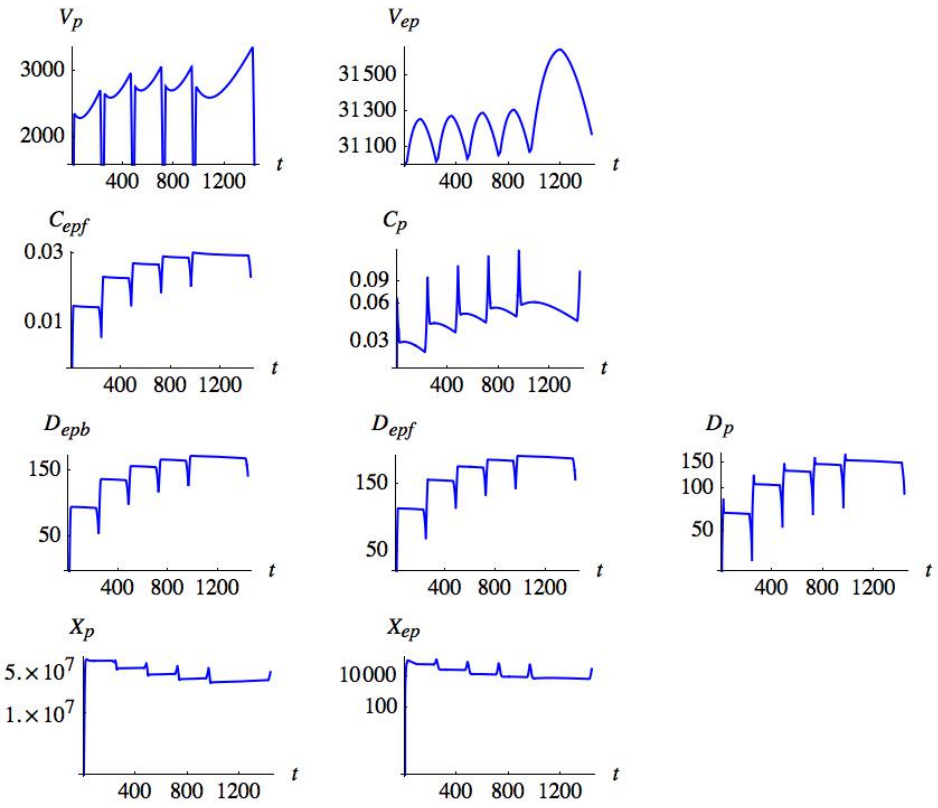

FIGURE 3. Plots of Volume of fluid distribution, drug concentrations, bound and free drug amounts, and bacteria counts in PC and EPC over 5 cycles of sequence (4,4,4,4,8) hours for one-day treatment.

6 exchanges, each exchange lasts between 3 to 8 hours. We realize that in this case the antibiotic level would no longer stay constant. Over a one-day treatment, we find the best situation to be the sequence (3,3,3,4,5,6) producing the smallest number of bacteria and the worst situation to be the sequence (8, 8, 8) giving the largest number of bacteria. The sequence (3,3,3,4,5,6) would correspond to the administration of a drug amount of 6 times 250mg while the second sequence of 3 exchanges would therefore give 3 times the drug amount, which is 50% less. After 3 days of treatment this result is reversed, to the contrary the sequence (8,8,8) unexpectedly yields the least amount of bacteria. We extend the analysis to seven days and show the results in Table 3.

4. **Discussion.** The model is used to calculate the total number of bacteria present in both peritoneal and extra-peritoneal cavities for various sequences of exchanges during one-day and one-week treatments. The effect of timing of long cycle versus short cycle is first considered. We observe that for both one-day and one-week treatments the best situation occurs when the long cycle is scheduled at the end of the day. We compute the reduction in percentage for both cases relative to the first sequence. We also realize that the efficiency of the drug is attained when

the drug concentration in the cavities reaches a certain level for a sufficient dose of antibiotic. Such level is achieved when all short cycles are scheduled first maximizing the amount of drug administered to 4 times 250 mg over the first 16 hours of treatment.

Secondly we studied the effect of the number and duration of cycles on the dynamics of the bacterial population. We performed the simulations for all possible sequence of exchanges where the number of exchanges per day can vary from 3 to 6, for one to seven consecutive days. We found that the results for one-day treatment are opposite to the results for one-week treatment. The sequence (8,8,8) that produces the greatest amount of bacteria over a one-day period, gives the least amount of bacteria over a 7-day period. We assign these contradictory results to the fact that the system reaches a steady state after three days with then reversed results.

For long-term treatment of at least 7 days, the use of a smaller number of exchanges per day reduces the dose of antibiotics given. This prescription would be more beneficial to the patient, since it lowers drug exposure and side effects. However long cycles and long dwell periods are in general, less tolerable by patients. Due to their flexibility and mobility advantages, CAPD treatments are often selected over APD treatments by patients remaining active. Since APD requires a patient to be connected to an automatic cycler which regulates the filling and draining of the abdomen therefore, prescriptions with short cycles may be more favorable than prescription with long cycles. There are also other medical factors to consider in addition to patient preferences. The choice of a particular mode of treatment may also depend on patient's medical performance, for example, whether the patient is a high or low transporter. Since the rapidity of the diffusion process between peritoneum membrane and blood supply can range from high to low depending on patient's medical characteristics. A low transporter would need longer dwelling periods and would do better using long exchanges, while a high transporter would select shorter cycle exchanges. There is obviously, a need for a more detailed investigation in order to reach a compromise between maximizing drug amount for best bacterial clearance, and increasing patient benefits by reducing drug exposure and duration of cycle exchanges.

5. **Conclusions.** We have proposed and discussed a mathematical model of treatment of peritonitis associated with peritoneal dialysis based exclusively on quantitative data. This work is among a few studies that are not heavily dependent on statistical analysis despite the complexity of the problem due to the influence of numerous factors of medical or personal nature affecting the PD process. Comparative analysis of the model outcomes for various modes of treatment parametrized by the number and duration of exchanges provides new insights in understanding of the benefits of specific antimicrobial treatments. Within our model we have presented a general description of computational aspects of peritonitis treatment and in this sense our model can be considered as a first step toward realizing the benefits of different approaches to therapy associated with peritoneal dialysis. CAPD treatment in general, consists of 4-6 short exchanges a day that last 4-6 hours each, unlike APD treatment that uses in general, 3-10 cycles of short duration at night. Presently, there is no strong evidence in the medical literature in selecting a particular method between CAPD and APD treatment as the most beneficial to patients with peritonitis. Our analysis provides a general frame of study to determine which

factors prevail for different conditions and provide an objective comparison of different modes of treatment in PDAP. Our approach allows the use of data from virtual patients characteristics which could be very helpful in realistic situations when in vivo measurements during PD process are not accessible. The model estimates for long-term treatment offer new insights that could benefit both patients and clinicians.

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Notation	Values	Description
C_0	.39 $\mu g/ml$	Initial drug concentration in serum [*]
C_{50}	0.477 $\mu g/ml$	Drug concentration producing a 50 % kill rate in serum [*]
D_{bag}	250 mg	Initial amount of drug in dialysate bag [5]
D_{epb0}	0 mg	Initial amount of bound drug in EPC [5]
D_{epf0}	0 mg	Initial amount of free drug in EPC [5]
D_{p0}	0 mg	Initial amount of drug in PC [5]
D_{pm}	250 mg	Maximum amount of drug in PC
D_{epm}	250 mg	Maximum amount of drug in EPC
k_1	0.6 $/min$	Diffusion/convection coefficient rate from PC to EPC
k_2	0.4 $/min$	Diffusion/convection coefficient rate from EPC to PC
k_{bf}	0.55 $/min$	Transfer coefficient rate from bound to free drug
k_{fb}	0.45 $/min$	Transfer coefficient rate from free to bound drug
k_D	0.02	Drug transport coefficient via lymphatic system
$Q_c(t)$	$\pm\lvert q_{cn} - q_{ct}\rvert$ ml/min	Intracellular water flow rate (half-cycle)
q_{cn}	0.85 ml/min	Intracellular flow rate from cell membranes into EPC
q_{ct}	0.8 ml/min	Intracellular flow rate from EPC into cell membranes
$Q_D(t)$	$Q_{dn}(t) - Q_{dt}(t)$ ml/min	Flow rate of liquid flowing in or out of dialysate bag [5]
$Q_{dn}(t)$	150 ml/min if $t < T_1$	Filling rate of liquid into PC from dialysate bag [5]
$Q_{dt}(t)$	120.75 ml/min if $t > T - T_2$	Drainage rate from PC into dialysate bag [5]
$Q_L(t)$	$Q_l + Q_f(t)$ ml/min	Sum of lymphatic and ultrafiltration rates
$Q_f(t)$	$q_{fm}(e^{-4t/T} - t/T)$ if $t > T_1$	Ultrafiltration flow rate for a T minute-cycle
q_{fm}	5.6 ml/min	Maximum value of ultrafiltration flow rate
Q_l	1.25 ml/min	Lymphatic flow rate [5]
Q_0	3 ml/min	Oral water flow rate [5]
$Q_U(t)$	0.7/ 1.3 ml/min	Renal elimination rate min/max value [5]
$Q_W(t)$	$Q_C(t) + Q_0$ ml/min	Intra and extra cellular water flow rate

Table 1: Model Parameters ([*]=Unpublished Data).

Notation	Values	Description
s_D	0.5	Bacteria transport coefficient from dialysate bag into PC
s_L	0.1	Bacteria transport coefficient via lymphatic system
s_U	0.01	Bacteria transport coefficient through renal elimination
T	240/480 min	Time period for a short/long cycle [3]
T_1	15 min	Filling time of PC [5]
T_2	20 min	Drainage time of PC [5]
T_m	T/2 min	Half-time period
$U(t-a)$	0 if $t < a$, 1 if $t \geq a$	Unit step function
V_{bag}	2250 ml	Volume of dialysate solution in bag [5]
V_{ep0}	31000 ml	Initial volume of fluid of distribution in EPC [5]
V_{p0}	50 ml	Initial volume of fluid of distribution in PC [3]
V_{res}	165 ml	Initial residual volume of fluid of distribution in PC [5]
V_{pres}	V_p at end of previous cycle	Residual volume of fluid of distribution in PC
X_{M1}	10^8	Maximum number of bacteria in PC [6]
X_{M2}	10^5	Maximum number of bacteria in EPC
X_{p0}	10^6	Initial number of bacteria in PC [6]
X_{ep0}	.0001	Initial number of bacteria in EPC
α	0.05776	Antibiotic action rate in serum [*]
α_0	0.25	Extra-cellular fraction coefficient in EPC [5]
ϵ_1	0.6 $/min$	Antibiotics killing coefficient rate in PC [*]
ϵ_2	0.5 $/min$	Antibiotics killing coefficient rate in EPC
γ_1	1.72	Hill coefficient in PC [*]
γ_2	2.04	Hill coefficient in EPC
μ_1	$0.553/min$	Bacterial growth coefficient rate in PC [*]
μ_2	$0.28/min$	Bacterial growth coefficient rate in EPC

Table 1 (continued) : Model Parameters.

Exchange Sequence	Bacteria count over 1 day	Percentage Decrease	Bacteria count over 7 days	Percentage Decrease
(8,4,4,4,4)	7.38993	0.0	30.1777	0.00
(4,8,4,4,4)	6.96917	5.69	29.7179	1.54
(4,4,8,4,4)	6.69568	9.39	29.4192	2.51
(4,4,4,8,4)	6.55516	11.3	29.2661	3.02
(4,4,4,4,8)	6.5439	11.4	29.2538	3.06

Table 2 : Effect of timing of 8-h cycle on bacteria count in units of 10^{10}.

Exchange Sequence	Bacteria count over 1 day	Percentage Increase	Bacteria count over 7 days	Percentage Decrease
(3,3,3,4,5,6)	6.12698	0.0	30.3791	0.00
(4,4,4,4,8)	6.5439	6.8	29.2538	3.7
(8,8,8)	7.74979	28.7	26.035	14.7

Table 3 : Effect of different cycles on bacteria count in units of 10^{10}.