

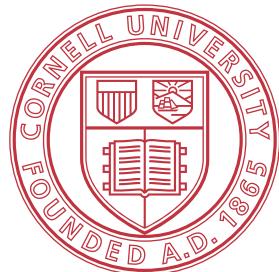
Towards a Personalized, State Aware Model of Trauma

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Introduction

Trauma is the leading cause of death and disability, surpassing all other causes combined, for persons 36 years old and younger [1], with hemorrhage accounting for 40% of all trauma deaths [2]. Control of bleeding is especially challenging in the presence of blood coagulation disorders, collectively known as coagulopathy. However, adverse outcomes associated with coagulopathy are not limited to death from acute blood loss. Organ dysfunction, multiple organ failure and increased susceptibility to sepsis [3] are all potential consequences of prolonged shock resulting from coagulopathy [4]. Following a wound, the immediate response of the body is to activate the coagulation cascade, which in turn generates a clot through the fibrinolysis network. Varnerlab has worked for 10 years on understanding the coagulation cascade, using both mechanistic models e.g., [5, 6], and more recently reduced order modeling approaches [7]. These models have also been used by the medical community [8, 9], and licensed by biopharma simulation companies such as Certara, to better understand this important cascade. However, recent studies have demonstrated that coagulation is only one component of the body's response to injury. Coagulation is integrated with inflammation, the autonomic nervous system and adaptive immunity through many factors including complement, a subsystem of innate immunity [10]. Thus, if we are to fully understand trauma, we must model these biochemical subsystems in addition to the physics of bleeding. Toward this challenge, we will develop a collection of reduced order models of blood biochemistry, as well as models which control heart rate and vessel dilation, and integrate these models with whole-body simulation approaches such as Physiologically Based Pharmacokinetic Models (PBPKs). My thesis work will be dived into three specific aims:

Aim 1: Develop a state-aware mathematical model of the human body. We will develop a model of the human body with a time dependent heart rate and blood pressure that considers the amount of blood that has been lost. From the heart rate, we will be able constrict or expand compartments based on the levels of vasoactive molecules.

Aim 2: Develop personalized models of trauma. We will allow for our model to be personalized based on height, weight, and gender and potentially other factors.

Aim 3: Predict the patient-specific efficacy of trauma interventions. With our personalized model, we will be able to model the effects of different fluid inputs, such as colloids or whole blood, and observe how the patient fares. We will also be able to see how the dosing schedule determines outcomes.

Significant previous work

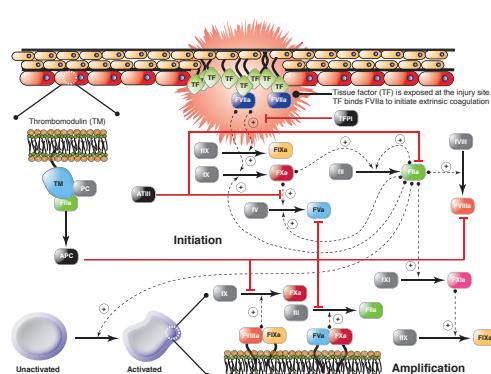


Fig. 1: Schematic of the extrinsic and intrinsic coagulation cascade. Upstream coagulation factors are activated by materials exposed following vessel injury which initiates thrombin production (fIIa) from prothrombin (fII). fIIa catalyzes its own activation (amplification), platelet activation, and its own inhibition by activated protein C (APC). APC and tissue factor pathway inhibitor (TFPI) inhibit initiation and amplification, while antithrombin III (ATIII) directly inhibits thrombin.

Mathematical modeling of coagulation and fibrinolysis. Wounds to the circulatory system activate the coagulation cascade, with factors (proteases) and platelets, a specialized type of blood cells playing key roles (Fig. 1). One protease, thrombin, is central to coagulation, and its generation can be divided into three phases: initiation, amplification, and termination [11, 12]. When a triggering event occurs, such as an injury to the circulatory system, initiation starts with the activation of factor VII (fVIIa), beginning the extrinsic portion of the cascade. The intrinsic and extrinsic cascades merge at the activation of factor X (fXa), and then a small amount of thrombin activates factors V and VIII, as well as platelets. The tenase and prothrombinase complexes can then form on the now ac-

tivated platelets, and these complexes amplify thrombogenesis by directly converting prothrombin to thrombin and by activating fX.

Thrombin formation can be inhibited at several points. Thrombomodulin prevents the formation of additional thrombin by binding to thrombin (preventing thrombin from activating any other factors), and the thrombin-thrombomodulin complex activates protein C. [17] Protein C, with its cofactor protein S, inactivates factors Va and VIIIa and inhibits the thrombogenesis process. [18] Antithrombin III binds to active factors, preventing them from further catalyzing the clotting process. Finally, termination occurs when all of the prothrombin available has been consumed, or a sufficient amount of thrombin has been rendered inactive by inhibitors, such as activated protein C or antithrombin III.

Activated thrombin plays a dual role in blood clot formation. First, it catalyzes the cleavage of fibrinogen to fibrin, a key component of a blood clot, thereby promoting clot formation. Activated thrombin also activates thrombin-activatable fibrinolysis inhibitor (TAFI), which inhibits the activity of plasmin, an important enzyme present in blood that degrades many blood plasma proteins, including fibrin clots. Counter balancing the role of activated thrombin is tissue plasminogen activator (tPA), which activates plasmin, thereby promoting the break down of blood clots. Thus, a delicate balance exists between activated thrombin and tPA that controls the rate of clot formation. Too much activated thrombin leads to hypo-fibrinolysis (excessive clot formation resulting in stroke or heart attack risk), while too little or excess tPA leads to hyper-fibrinolysis (inadequate clot formation resulting in increased, sometimes catastrophic bleeding). Tanaka and Chapin [20, 21] provide excellent reviews of coagulation and fibrinolysis.

Many previous models described coagulation using systems of nonlinear ordinary differential equations, using mass action or other, more complex kinetics [22–26]. Varnerlab built upon earlier studies [27–29] to produce mechanistic ordinary differential equation based models of coagulation [5, 6]. Models exist for specific aspects of coagulation: thrombin mediated clot formation [30], fibrinolysis [31], platelet biochemistry [32], transport inside of clots [33], as well as models of clot formation at different scales[34, 35]. Papadopoulos et al created a reduced order model for predicting thrombin generation [36], which uses only four differential equations. This reduced order model succeeded in predicting thrombin generation curves, but does not include key inhibitors of thrombin generation.

The central challenge of modeling coagulation or other biochemical cascades important in trauma is estimation of model parameters, and dealing with unknown biochemical mechanisms. Toward this challenge, Varnerlab has developed a reduced order modeling approach which integrates logical rules, which describe interactions that may not be well understood, with traditional ordinary differential equation modeling. In this approach, the abundance of species i (x_i) is governed by:

$$\frac{1}{\tau_i} \frac{dx_i}{dt} = \sum_{j=1}^{\mathcal{R}} \sigma_{ij} r_j(\mathbf{x}, \mathbf{k}) - k_{d,i} x_i \quad i = 1, \dots, \mathcal{M} \quad (1)$$

where \mathcal{R} and \mathcal{M} denote the number of reactions and species in the model, and $k_{d,i}$ denotes a degradation constant for species i . The quantity σ_{ij} denotes the stoichiometric coefficient for species i in reaction j , $r_j(\mathbf{x}, \epsilon, \mathbf{k})$ denotes the rate of reaction j , and \mathbf{k} ($\mathcal{K} \times 1$) denotes the unknown kinetic parameter vector. If $\sigma_{ij} > 0$, species i is produced by reaction j , if $\sigma_{ij} < 0$, species i is consumed by reaction j , while $\sigma_{ij} = 0$ indicates species i is not connected with reaction j . Species balances were subject to the initial conditions $\mathbf{x}(t_0) = \mathbf{x}_0$. The reaction rate was written as the product of a kinetic term (\bar{r}_j) and a control term (v_j), $r_j(\mathbf{x}, \mathbf{k}) = \bar{r}_j v_j$. The control term $0 \leq v_j \leq 1$ depended upon the combination of factors which influenced rate process j . For each rate, we used a rule-based approach to select from competing control factors. If rate j was influenced by

$1, \dots, m$ factors, we modeled this relationship as $v_j = \mathcal{I}_j(f_{1j}(\cdot), \dots, f_{mj}(\cdot))$ where $0 \leq f_{ij}(\cdot) \leq 1$ denotes a regulatory transfer function quantifying the influence of factor i on rate j . The function $\mathcal{I}_j(\cdot)$ is an integration rule which maps the output of regulatory transfer functions into a control variable.

Physiologically Based Pharmacokinetic Models (PBPK). PBPK models are standard tools to model the physical disposition of blood constituents in the body. PBPK models are composed of a collection of well-mixed organ compartment models (of variable complexity) interconnected by a circulatory system (Fig. 2). Classically, PBPK models were developed to predict the tissue distribution of therapeutic agents or toxins [37] and these models readily allow the assimilation of potentially important clinical information such as the demographic and physical characteristics of patients, and naturally incorporate key clinical information such as cardiac output, dissolved oxygen levels, blood flow rates to well- and poorly-perfused organs, and pulmonary function. Thus, PBPK models are ideal candidates to simulate clinically important physical characteristics of patients. However, PBPK models are typically not used in combination with detailed models of blood biochemistry, e.g., coagulation or immune system models, or nervous systems models that modulate heart or inhalation rates.

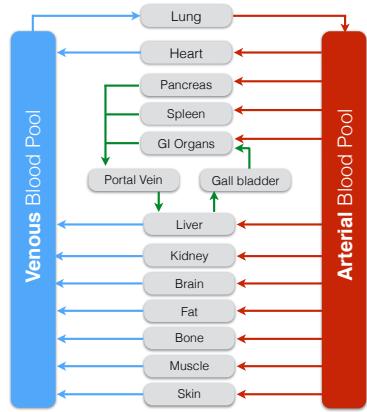


Fig. 2: A PBPK with many compartments. Blood flows from the arterial blood pool, through one of the organ compartments, and into the venous blood pool.

Current trauma models either simplify the body or the coagulation process. For example, Ho et al. developed a model that considered blood to be two distinct parts, either hematocrit or plasma, and assumed the rate of fluid loss was the same as the rate of fluid replacement. They did not model the coagulation process; instead, they lumped all of the coagulation factors into one variable, which they correlated with prothrombin time [38]. Their model provides guidance on the ratio of fresh frozen plasma (FFP) to packed red blood cells (PRBC) that patients with excessive blood loss should receive. A slightly more complex model by Hirshberg et al. modeled blood as having three compartments: red cells, plasma, and water, and allowed flow between these compartments based on systolic blood pressure [39]. They used prothrombin time to quantify if a patient was at risk for dilutional coagulopathy, and did not consider the biological mechanisms behind coagulation. A model without compartments, but containing more physiological functions was developed by Simpson et al. [40]. Simpson's model allows for both blood pressure and bleed out rate to change over time, with

the bleed out rate decreasing as blood pressure decreases. This model predicts hematocrit levels over time, but not the levels of specific proteins. Reisner et al. re-purposed their model of the cardiovascular system (which was originally created to predict how the cardiovascular system responds to orthostatic stress) to study hemodynamic responses to haemorrhage [41]. Their model includes the heart and pulmonary circulation as well as four peripheral tissue compartments representing the upper body, legs, viscera and kidneys, each of which received the same fraction of the cardiac output. They modeled blood by separating it into two components: red blood cells and plasma. This model includes transcapillary fluid exchange and lymphatic flow but groups all proteins together.

Modeling of heart rate. A key parameter in the PBPK model is cardiac output (CO). Cardiac output is the product of the stroke volume (amount of blood pumped per beat) and the heart rate, which can be modulated by a variety of stimuli. Olufsen and Ottesen have developed several models of heart rate regulation [42–45]. Heart rate is determined, in part, by the sympathetic

and parasympathetic nervous system. Sympathetic nervous system stimulation releases the hormones epinephrine and norepinephrine into the circulation, which increase heart rate. On the other hand, the parasympathetic system releases acetylcholine which decreases heart rate. These two systems, often described as an accelerator and a brake, are not independent. Rather, they interact through second messengers cAMP (cyclic adenosine monophosphate) and cGMP (cyclic guanosine monophosphate) [46]. Heart rate is also influenced by the baroreflex system consisting of baroreceptors, which are tension sensitive nerve endings found in the circulatory system [43]. When baroreceptors sense a pressure change, they modulate in the frequency of nerve activity. When pressure (and stretch) rapidly increase, so does the baroreceptor firing rate [47]. The effect of this signal is not instantaneous, rather, there is a time delay on the order of seconds before the sympathetic and parasympathetic nervous systems respond [43]. These models use the baroreflex system and the concentrations of acetylcholine and norepinephrine to predict heart rate. They assume changes in arterial wall stretch are proportionate to filtered blood pressure, $\dot{p} = \alpha(-\bar{p} + p)$ where α is a gain, \bar{p} is the filtered blood pressure, and p is the patient's measured blood pressure. From \bar{p} , we can predict the nervous system firing rate, $n = \sum_i n_i + N$, $i = 1, 2$

where N is a baseline firing rate and n_i corresponds to the firing rate of nerve fibers of type i . The firing rates for nerves of type i are computed as:

$$\frac{dn_i}{dt} = \kappa_i \frac{d\bar{p}}{dt} \frac{n(M - n)}{(M/2)^2} - \frac{n_i}{\tau_i}, i = 1, 2 \quad (2)$$

where M is the maximum firing rate, and τ_i is the time scale for nerves of type i . The firing rate information is compiled by the central nervous system, which then determines the sympathetic and parasympathetic outputs, f_{sym} and f_{par} , respectively. The parasympathetic output is given by $f_{par} = n/M$, while sympathetic output takes the form:

$$f_{sym} = \frac{1 - n(t - \tau_d)/M}{1 + \beta f_{par}} \quad (3)$$

With these outputs, we can determine the dimensionless concentrations of acetylcholine, c_{ach} and noradrenaline, c_{nor} :

$$\frac{dc_j}{dt} = \frac{f_j - c_j}{\tau_j} \quad (4)$$

where each τ_j represents a time scale. Finally, the heart rate is calculated from h_0 , the intrinsic heart rate, and m_{nor} and m_{ach} , which are weights for the contributions of acetylcholine and norepinephrine to heart rate $h = h_0(1 + m_{nor}c_{nor} - m_{ach}c_{ach})$.

Research plan

Aim 1: Develop a state-aware mathematical model of the human body. (Fall 2016-Spring 2017) The objective of this aim is to create a model of the human body with a heart rate and blood pressure that changes with the patient's blood volume. Toward this aim, we have implemented a model that predicts heart rate based on blood pressure. We then optimized the parameters used in this model, which greatly improved the accuracy of the predictions.

Reduced order modeling of biochemical trauma cascade. A reduced order model of the trauma cascade allows us to capture the essence of the biological processes occurring while reducing the number of differential equations that must be solved. This reduction is useful in PBPK modeling, where the differential equations governing the behaviour of species must be solved in each compartment.

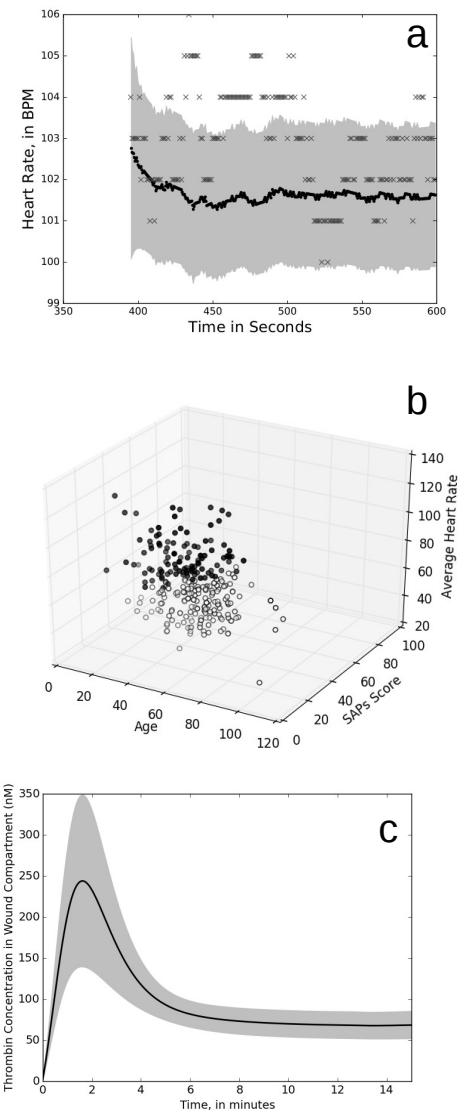


Fig. 3: Simulation of heart rate model is shown in subfigure A. The x represent the true data, the black dots represent the average model performance over the 10 different parameter sets, and the grey is a 95% confidence interval. Subfigure shows the clustering of the MIMIC patients. Subfigure C shows the concentration of thrombin in the wound compartment of the PBPK, with the black being the mean concentration and the grey showing a 95% confidence interval for collection of patient with different organ volumes and initial concentrations.

rate increases dramatically [53]. During all three phases, the concentrations of adrenaline, norepinephrine, and vasopressin rise, but then decrease once blood is transfused. Using the blood pressure tracks from MIMIC II, we used Olufsen's and Ottsen's model [45] to predict heart rate within the PBPK model. We used the Nelder Mead algorithm to estimate parameters that better

A reduced order model of fibrinolysis is currently under development by the Varner group. This model expands on the reduced order coagulation model by Sagar et al. by including 18 species. We will validate the reduced order fibrinolysis model using ROTEM, TEG, and FIIa time series measurements taken at the University of Vermont. Incorporating it into PBPK will allow us to study both coagulopathy and DIC. The larger reduced order model allows us to track more species, providing us with more points of comparison between the model and experimental data, for better estimation of kinetic parameters. The development of a reduced order model of complement, a component of the immune response, is also underway. In its current form, this small model predicted the overall trends of C3a and C5a concentration, but the C3 dynamics were too fast. By changing how tickover (the spontaneous hydrolysis of C3) is described in the model, we can better capture the dynamics of C3 formation. We will compare the complement model's prediction to experimental data to insure that it accurately describes the dynamics of the system [48]. Although complement is a pathway traditionally associated with the immune response, it activated following trauma, and shifts the balance towards coagulation by activating platelets and increasing tissue factor expression [49]. By including a complement in our trauma model, we will be able to capture the interactions between complement and coagulation, which may prove important to accurately describe DIC. Furthermore, we will be able model platelet activation, as both C3 and C5b-9 alter platelet behavior [50].

Identification of a heart rate model for trauma patients. We estimated heart rate model parameters using 273 patients from the MIMIC-II/III, a freely-available database comprising deidentified health-related data associated with over forty thousand patients who stayed in critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012 [51]. When less than 10% of blood volume has been lost, the baroreflex is initiated as pressure has dropped to increase heart rate [52]. After approximately 10% of blood volume has been lost, heart rate begins to decrease, as does blood pressure. When blood loss approaches 30% of blood volume, heart

fit the MIMIC II data. Additionally, we used k-means clustering to group the patients into two clusters, based on age, average heart rate, and SAPS (Simplified Acute Physiology) score. We then used the JuPOETS multiobjective optimization package [54] to generate families of parameters for the two clusters (Fig. 3). The estimated parameters reduced the total mean squared error by more than two-thirds. Furthermore, we used the acetylcholine and noradrenaline concentrations predicted by this model to vasodilate and constrict the arterial and venous blood pools. The arterial and venous blood are constricted if the noradrenaline concentration is above a threshold value, and dilated if the acetylcholine concentration is above a threshold value. The expansion and contraction of the compartments was capped at 125% and 75% of their resting values, respectively to prevent unphysical volume changes. The degree of volume change was based on previous experimental data on volume change as a function of a concentration of acetylcholine and noradrenaline [55, 56]. In general, adding the heart rate change and vasoconstrictive factors to the model slightly shifts the curves, but does not alter their overall shape.

Incorporating reduced order biochemical models into the PBPK framework. We constructed an eight compartment model of the human body, using the Kwatee code generation system [57]. In this model, blood flowed from a venous pool, to the heart, through the lungs, back through the heart, and into an arterial blood pool. Blood then passed from the arteries through the liver, kidney, or bulk to the veins. All of the proteins flowed freely between compartments, except for thrombomodulin and trigger, which are bound to cell membranes [17]. We simulated a small wound connected to the arterial blood pool, with a volume of 0.5% of the total blood volume. Coagulation dynamics were modeled using the reduced order model constructed by Sagar et al. [58]. In the reduced order model, trigger (which biologically corresponds to the tissue factor-FVIIa complex) activated thrombin. Thrombin then catalyzed its own activation, as well as the activation of protein C, which inhibited the activation of thrombin. Antithrombin complexed with thrombin and deactivated it. We ran the model in a collection of different patients, each with slightly different organ volumes and initial concentrations, with the thrombin concentration in the wound compartment shown in Figure 3c. The patient is bleeding out at a constant rate of 10.5 mL/min, which would lead to complete exsanguination in less than ten hours. As blood volume diminishes, the heart rate of the patient increases. The blood loss comes from the arterial and bulk compartments, leading to a rise in the concentration of thrombomodulin in those compartments, as their volume is decreasing while the amount of thrombomodulin present remains constant.

Proposed studies. With the aim to develop a model of acute haemorrhage and resuscitation, Menezes created a method of estimating blood pressure as a function of the blood volume lost and allowing the bleed out rate to vary as a function of blood pressure [59]. His model also allows total blood volume to change based on trans-capillary refilling, the process through which fluid moves from interstitial space into the blood due to a change in pressure. We will use his model to predict blood pressure as a function of blood loss, and combine it with the previously described heart rate prediction model to create our state aware body. Johansson et al. collected extremely detailed bloodwork on adult trauma patients at a level one trauma center, including thrombin/antithrombin-complexes, antithrombin, protein C, fibrinogen, FXIII levels as well as activated partial thromboplastin time [60] approximately one hour after injury. We can compare our model predictions to Johansson's data to confirm that the model predictions are valid.

Expected outcomes, potential pitfalls and alternative approaches. We expect Aim 1 will produce a model body with time varying heart rate and blood pressure with the reduced order models of fibrinolysis, coagulation, and complement running in each compartment. However, if the reduced order models fail to capture the combined dynamics of coagulation, fibrinolysis, and complement, we can consider alternative, more complex ODE or PDE based models of each process. Should

the combination of heart rate and blood pressure models fail to give a sufficient description of the human body, a more complex model, such as the one developed by the SAPHIR project will be implemented [61]. We expect our approach will be successful, as it will build upon previously proven models.

Aim 2: Develop personalized models of trauma. (For A exam, Summer 2017-Summer 2018)

Proposed studies. To capture a spectrum of responses in a model, it is necessary to consider the variation in physiological parameters between individuals. The P³M project has developed a large set of bodies that can be used to test PBPK models [62]. This set of bodies includes both organ masses as well as perfusion rates for male and female bodies. We can use this spectrum of bodies to compare coagulation and fibrinolysis in bodies of varying size and composition to see the range of responses and use the correlations developed by the P³M model to generate organ volumes based on the height and weight of individuals. We also need to capture the biochemical differences between individuals. Studies have associated genes with circulating fibrinogen levels [63], protein C levels [64], activated partial thromboplastin time and prothrombin time [65], and thrombosis [66]. We can combine this information with the sequences available from the 1000 Genomes project to generate differing initial concentrations and rate constants for individuals.

Expected outcomes, potential pitfalls and alternative approaches. At this point, the model will take in patient physiological data to produce more accurate predictions of how this patient will respond to traumatic injury. If the proposed method of using genetic information proves unfeasible, the Plasma Proteome Database includes concentrations of many proteins found in blood plasma and serum [67]. We can use these concentrations as an average, and then generate a distribution of concentrations to simulate the population.

Aim 3: Predict the patient-specific efficacy of trauma interventions. (Beyond A exam)

Proposed studies. Current treatment for trauma patients requiring massive transfusion is crystalloids, followed by red blood cells, and then plasma and platelets, but newer military studies have shown that outcomes improve if patients receive plasma and platelets earlier while minimizing the amount of crystalloids [68]. With our personalized model, we can test to see how patient survival changes under both treatment schemes. We can also examine patient survival if clotting factor concentrates are given, as is currently the treatment in Europe [69].

Expected outcomes, potential pitfalls and alternative approaches. We expect that the outcome of aim 3 will provide support for a fluid treatment schedule and dosage for trauma patients. It may turn out that there is no one universally best treatment, that outcomes are highly dependant on physiological and genetic factors. Physiological factors can easily be accessed at the time of hospital arrival, but genetic factors take longer to measure, potentially prohibiting using that mode of personalization if rapid output is necessary. Although our model will consider both physiological and biochemical processes, it is possible that its treatment recommendations may differ from those in the literature due to a mechanism not included in the model. If that is the case, and a model for the mechanism is available and easily implementable, it will be included in the model.

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