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EXPERIMENTAL STUDIES

PERSONALIZATION OF A COMPUTATIONAL SYSTEMS BIOLOGY MODEL OF BLOOD PLATELET CALCIUM SIGNALING

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Anuclear blood cells, platelets, are the basis for the formation of blood clots in human vessels. While antiplatelet therapy is most often used after ischemic events, there is a need for its personalization due to the limited effectiveness and risks of bleeding. Previously, we developed a series of computational models to describe intracellular platelet signaling and a set of experimental methods to characterize the platelets of a given patient. To build a personalized model of platelet signaling, we also conducted research on platelet proteomics. The aim of this study was to personalize the central module of intracellular platelet signaling responsible for the formation of calcium oscillations in response to activation. The model consists of 26 ordinary differential equations. To personalize the model, proteomics data were used and unknown model parameters were selected based on experimental data on the shape and frequency of calcium oscillations in single platelets. As a result of the study, it has been shown that the key personalized parameters of the platelet oscillatory response are the degree of asymmetry of a single calcium spike and the maximum frequency of oscillations. Based on the listed experimentally determined parameters and proteomics data, an algorithm for personalization of the model has been proposed. Here we considered three healthy pediatric donors of different ages. Based on the models, personal curves of platelet calcium response to activation were obtained. The analysis of the models has shown that while there is a large heterogeneity of individual indicators of intracellular signaling, such as the activity of calcium pumps (SERCA) and inositoltriphosphate (IP_3) receptors (IP_3R), these indicators compensate each other in each donors. This observation is confirmed by the analysis of proteomics data from 15 healthy patients: this analysis demonstrates a correlation between the total amount of SERCA and IP_3R. Thus, several new features of human platelet calcium signaling are shown and an algorithm for personalizing its model is proposed.

Key words: platelets; calcium signaling; inositol-3-phosphate receptor; computational modeling

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INTRODUCTION

Platelets are specialized disc-shaped anucleated blood cells about 2–4 microns in diameter and a thickness of about 0.5 microns [1]. The peculiar structure of platelets is characterized by the absence of a nucleus and the presence of numerous plasma membrane invaginations, known as an open canalicular system (OCS). These invaginations are thought to provide additional cell surface area for shape changes and the formation of pseudopods in response to activation [2]. Platelets also contain a dense tubular system (DTS), several mitochondria and a large number of granules that are secreted into the extracellular space when the platelet is activated [3].

To perform their main function, which is to react to bleeding from blood vessel injury by clumping, platelets must be activated (Fig. 1a). Platelets are activated both upon contact with the intercellular matrix components (in case of endothelial damage) and upon activation induced by ADP, adrenaline, serotonin, thrombin, etc. This triggers an intracellular signaling cascade, including calcium release from intracellular stores [2]. Most platelet activators act on G-protein coupled receptors, causing subsequent activation of phospholipase C (PLC; in human platelets the β isoform of PLC predominates [4]). This enzyme hydrolyzes phosphoinositide-4,5-bisphosphate to inositol-trisphosphate (IP_3) and 1,2-diacylglycerol [1, 5]. Since platelets lack ryanodine receptors calcium output from intracellular stores is completely determined by IP_3 receptor channels (IP_3R), and a decrease in calcium concentration in the cytosol is supported by SERCA ATPases (sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase) [5]. Studies of calcium signaling in single cells have shown that an increase in calcium concentration during platelet activation occurs, in the form of non-harmonic oscillations, the so-called spikes, rather than uniformly [6, 7]. Calcium signaling triggers integrin activation, shape change, granule secretion [8, 9], and platelet necrotic-like death [6].

Previously, we developed a series of computational models to describe intracellular platelet signaling, a “virtual” platelet which included all key activation processes [10]: calcium signaling from PAR1 leading to mitochondrial collapse [5], accounting for the heterogeneity of healthy donors

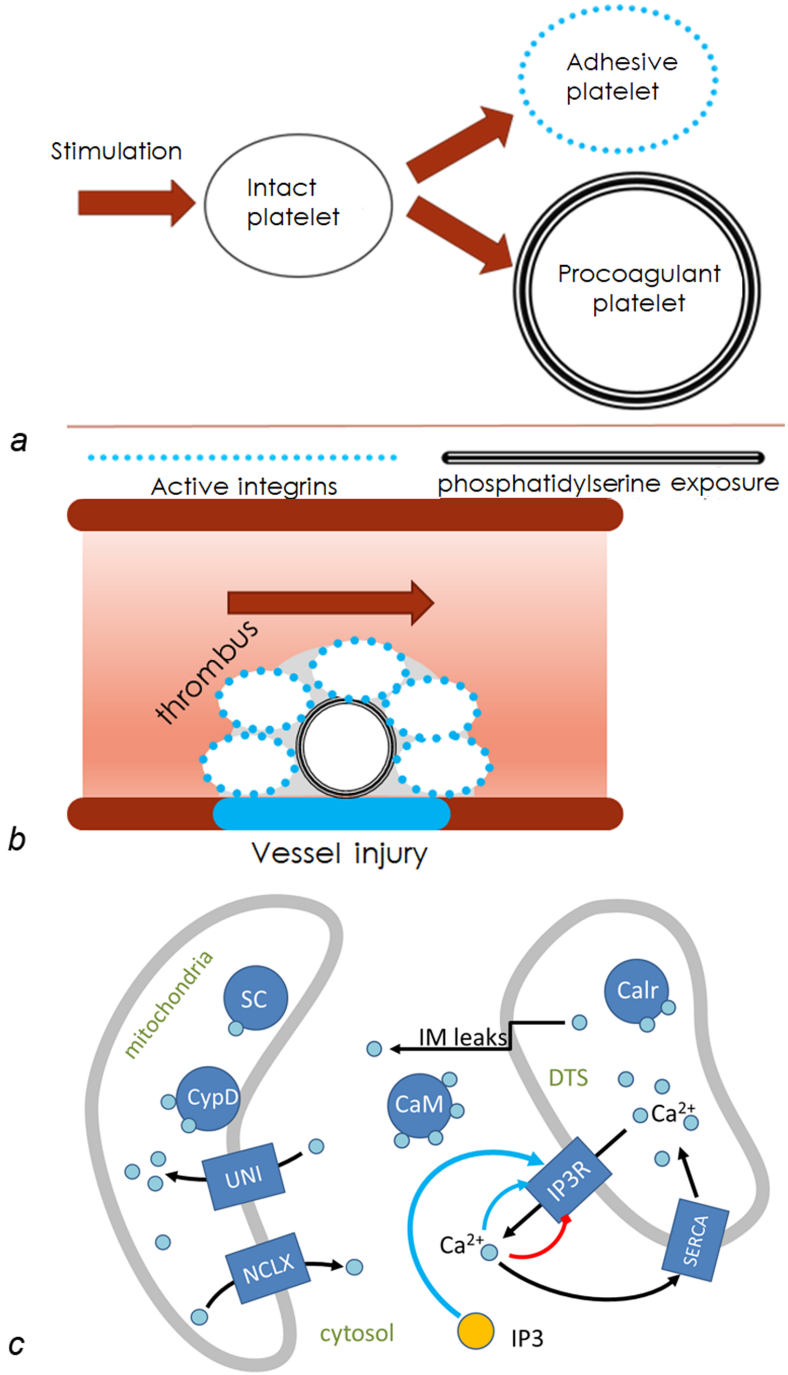

Figure 1. Schematic representation of platelet activation. Damage to the vessel leads to contact of several insoluble (collagen, fibronectin) and soluble (ADP) activators with intact platelets. (**a**) An intact platelet, upon contact with an activator (stimulus), passes either into a proaggregatory state (due to the activation of integrin proteins on its surface, allowing the formation of protein bridges between cells), or into a procoagulant state (due to exposure to a relatively negatively charged phospholipid phosphotidylserine on the outer side of the membrane; this catalyzes the clotting of blood plasma – coagulation). (**b**) Upon contact with the site of injury, aggregatory platelets adhere to the vessel wall and aggregate with each other; the procoagulant platelets cause plasma clotting and "cementation" of the platelet aggregate (indicated in gray). (**c**) Platelet activation leads to the release of inositol-trisphosphate (IP_3) into the cytosol. IP_3 binds to its receptors (IP_3R) in the ER (DTS) membrane, opening channels for the calcium release, which is usually contained in DTS due to the action of SERCA (sarcoplasmic/endoplasmic reticulum calcium ATPase). In DTS, calcium can be buffered by various agents, including calreticulin (Calr). In the cytosol, calmodulin (CaM) plays a role of the calcium buffer. An increase in the cytosolic calcium concentration leads to the opening of mitochondrial uniporters (UNI) and the entry of calcium into the mitochondria, where it is buffered by various proteins, including cyclophilin D (CyD) and the calcium-binding protein SCaMC (SC). Calcium is excreted from the mitochondria by the sodium-calcium exchanger (NCLX). Gray (colored) arrows indicate activation/inhibition processes, black arrows indicate substance flows. The color version of the figure is available in the electronic version of the article.

due to two thrombin receptors [11], ADP-induced activation, cAMP-dependent signaling and its interaction with calcium [12], tyrosine kinase signaling [13, 14], the role of multiple mitochondria and their connection with metabolism [6, 15, 16], and integrin activation [9]. In addition, a set of experimental approaches was developed to characterize calcium signaling in single platelets [13, 17, 18] and in platelet suspension [9, 19], as well as platelet protein composition using proteomics [20]. In all these studies, a similar set of patterns was recognized in the experimental assessment of platelet parameters and their functional response in healthy donors. According to cytometry data [9, 19], the size of platelets and the level of fibrinogen binding by platelets within the same patient can vary by an order of magnitude; however, the average size differs by 2–4 times among healthy donors. Meanwhile, calcium mobilization in response to activation varies by no more than 20–30% [9, 16] even in patients. Previously, we showed that the variation of functional responses in the population may be associated with polymorphisms of platelet receptors for thrombin [11] and collagen [14]. Also, for patients with Wiskott-Aldrich syndrome, we have shown that the ER/cytosol volume ratio plays a fundamental role in platelet activation [16]. Thus, it can be assumed that the personalization of the platelet response can be carried out by estimating the amount of proteins.

The aim of this study was to develop and validate a methodological approach to personalizing a computational model of human platelet calcium signaling with parameterization based on experimental observations of the dynamics of calcium signaling in response to stimulation and proteomics data.

MATERIAL AND METHODS

To describe calcium signaling, we used the models described earlier [5, 21] with the addition of calcium buffering proteins — calmodulin, calreticulin, etc. Using ordinary differential equations the model describes the behavior of 26 different compounds. The system of ordinary differential equations is integrated using the LSODA method [22] implemented in the COPASI software [23]. A detailed description of the model and the integration method are available in Supplementary Materials S1 and Tables S1 and S2. The parameter estimation was carried out by the Evolutionary Strategy method [24], implemented in the COPASI software [23]. The method parameters were selected by default, and the intermediate results (values of the objective function and deviations from the experiment) are presented in Supplementary Materials S2 and Tables S3 and S4.

Experiments on the dynamics of calcium signaling in single platelets were carried out using the method described earlier [13, 17, 18, 21]. Proteomics data are publicly available as online supplement for the manuscript [20].

RESULTS

Determination of the shape of platelet single calcium spike

Figure 2a are shows a typical response of a single platelet to ADP activation. The shape features of calcium peaks were analyzed by calculating the growth and decline rates for each single peak. For this purpose, we used a technique similar to that in the CaSiAn software package [25], originally developed to analyze the dynamics of calcium in neurons. Calcium peaks in the time series were identified as local maxima, with their boundaries defined by the absolute minima between adjacent peaks. Linear interpolation was then used to identify the points lying at two tenths of the peak height relative to the basal signal level. The growth and decline rates were calculated as the tangential coefficients of the lines drawn through the peak and one of the found points. Given that peak amplitudes varied across donors by two or more times, peak growth and decline times were chosen as the main

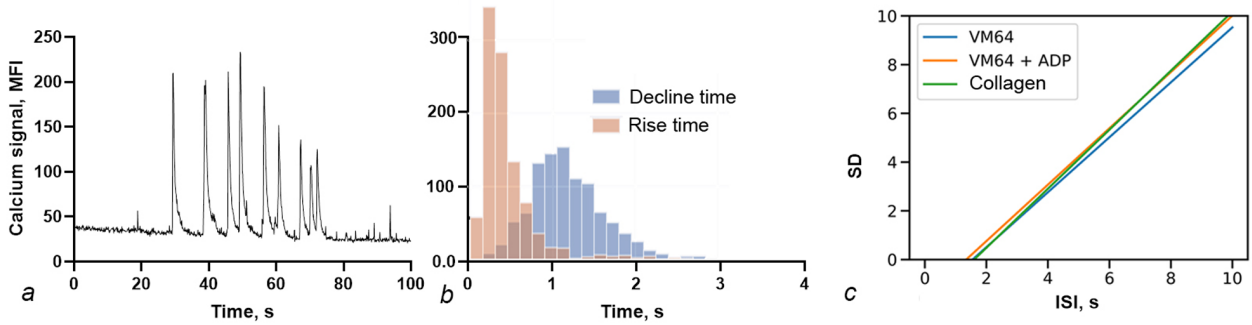

Figure 2. Properties of human platelet calcium oscillations. (**a**) The typical response of an immobilized platelet to ADP activation (borrowed from our previous study) [21].(**b**) A histogram of the growth and decline rates of calcium peaks in human platelets. (**c**) The dependence of the standard deviation of the peak intervals on the average for the peak intervals. The process of the appearance of calcium peaks is Poisson with a deterministic minimum distance between the peaks. The equality of the angles of inclination of the lines suggest the commonality of the mechanisms of the occurrence of calcium peaks in platelets spread on antibodies to CD31 (VM64), activated by 10 μM ADP (VM64+ADP) and activated by collagen.

quantitative characteristics. These distributions are shown in Figure 2b. The average growth time of the calcium peak was 0.51±0.65 s, the average decline time was 1.21±0.54 s. The average ratio of the growth rate to the decline rate was 3.5±2.2.

Since platelet calcium oscillations are stochastic [5, 6], it is not possible to determine their frequency. To characterize patient-specific responses, we used the approach proposed by Skupin and Falcke. They consider calcium spike occurrences as a non-stationary Poisson process [26]. Their main idea is that the peak interval (ISI) in various excitable cells consists of a constant T and a random ξ, while ξ is a random variable from a certain Poisson distribution [26, 27], and, consequently, the mathematical expectation of a random variable is equal to its standard deviation.

In platelets, the standard deviation shows a linear dependence on the average ISI (Fig. 2b). This observation supports the Poisson nature of calcium spikes occurrences in platelets: when peaks are infrequent, they appear more randomly, while activation-induced increases in spike frequency bring greater regularity. It is noteworthy that this process does not depend on the method of cell activation, since the slopes of the lines on the graphs are statistically indistinguishable. According to [28], the slope on such graphs reflects the rate of calcium storage reloading, and different slopes would indicate fundamentally different mechanisms for generating calcium oscillations in platelets. Consequently, there is a commom mechanism that cause calcium oscillations, both during platelet activation via the tyrosine kinase pathway by collagen and the G-protein-coupled pathway. According to this graph, it is also possible to determine the minimum interspike interval (1.6±0.4 s) as corresponding to the zero standard deviation.

Personalization of the Calcium Module of the Platelet Intracellular Signaling Model

A previously proposed model [5] was used to describe calcium signaling in platelets, describing the release of calcium from intracellular stores under the action of IP_3 through IP_3R2 and replenishment of stores with SERCA of types 2b and 3. In addition, it was previously shown [21] that signal asymmetry was associated with both receptor clustering and ion buffering in the cytosol, intracellular storages and mitochondria. Therefore, calcium buffer proteins calmodulin [29], calreticulin [30], endoplasmin [31], GRP78 [32], and mitochondrial sensors were added to the model [33, 34]. The scheme of the main processes described by the model is shown in Figure 1c. The list of proteins is presented in Tables 1 and S1.

To personalize the model, we used the following algorithm. First, the volumes of the cytosol, intracellular storages and mitochondria were estimated, as it was previously shown that the volume ratio could be important [19]. Reference proteins presented in proteomics were used to estimate these volumes (Table 1). After this, protein quantity was set to the average amount obtained in the proteomic analysis [20], or, in the absence of protein, the reference amount [35]. In this work, we used data for three pediatric healthy donors from [20]. For each donor, the analysis described in the first part of the article was carried out, based on previously obtained [17] data on calcium oscillations in single platelets. Namely, the average times of spike rise and decline were obtained, a characteristic single spike was derived (Fig. 3, left) and the minimum peak interval corresponding to the zero standard deviation was determined (Fig. 3, right). After that, parameter estimation methods were used to select unknown

Table 1. The number of molecules of key calcium signaling proteins per platelet based on proteomics data [35]

Protein/gene (comment)	Literature data*	Donor 1, 2 years old	Donor 2, 14 years old	Donor 3, 16 years old
IP3R1/ITPR1_HUMAN	2400	4663	n/d	n/d
IP3R2/ITPR2_HUMAN	1700	2610	n/d	n/d
IP3R3/ITPR3_HUMAN	750	n/d	n/d	n/d
SERCA2b/AT2A2_HUMAN	9000	26569	12053	37876
SERCA3a/AT2A3_HUMAN	16300	51624	14707	49588
Calmodulin/CALM_HUMAN (Cytosol calcium buffering)	15600	n/d	n/d	n/d
ERP29_HUMAN (DTS volume reference)	5900	21809	7753	33151
ERP44_HUMAN (DTS volume reference)	4400	24585	14000	33089
ATPD_HUMAN (Mitochondria volume reference)	2800	11661	31069	73690
ATPA_HUMAN (Mitochondria volume reference)	14700	52976	19870	58178
ACTN1_HUMAN (Cytosol volume reference)	92100	120259	57009	141311
TBA4A_HUMAN (Cytosol volume reference)	185000	100476	33220	116309
MCU_HUMAN/C109A_HUMAN	5900	19526	4677	26103
CALR_HUMAN (DTS calcium buffering)	20300	51684	26780	67005
ENPL_HUMAN (DTS calcium buffering)	14400	43555	19537	59864
BIP_HUMAN (DTS calcium buffering)	27900	64928	25630	76352
PPIF_HUMAN (Matrix calcium buffering)	19100	33428	n/d	26404
SCMC1_HUMAN (Matrix calcium buffering)	2200	n/d	n/d	n/d

*Data for this table were taken from [35].

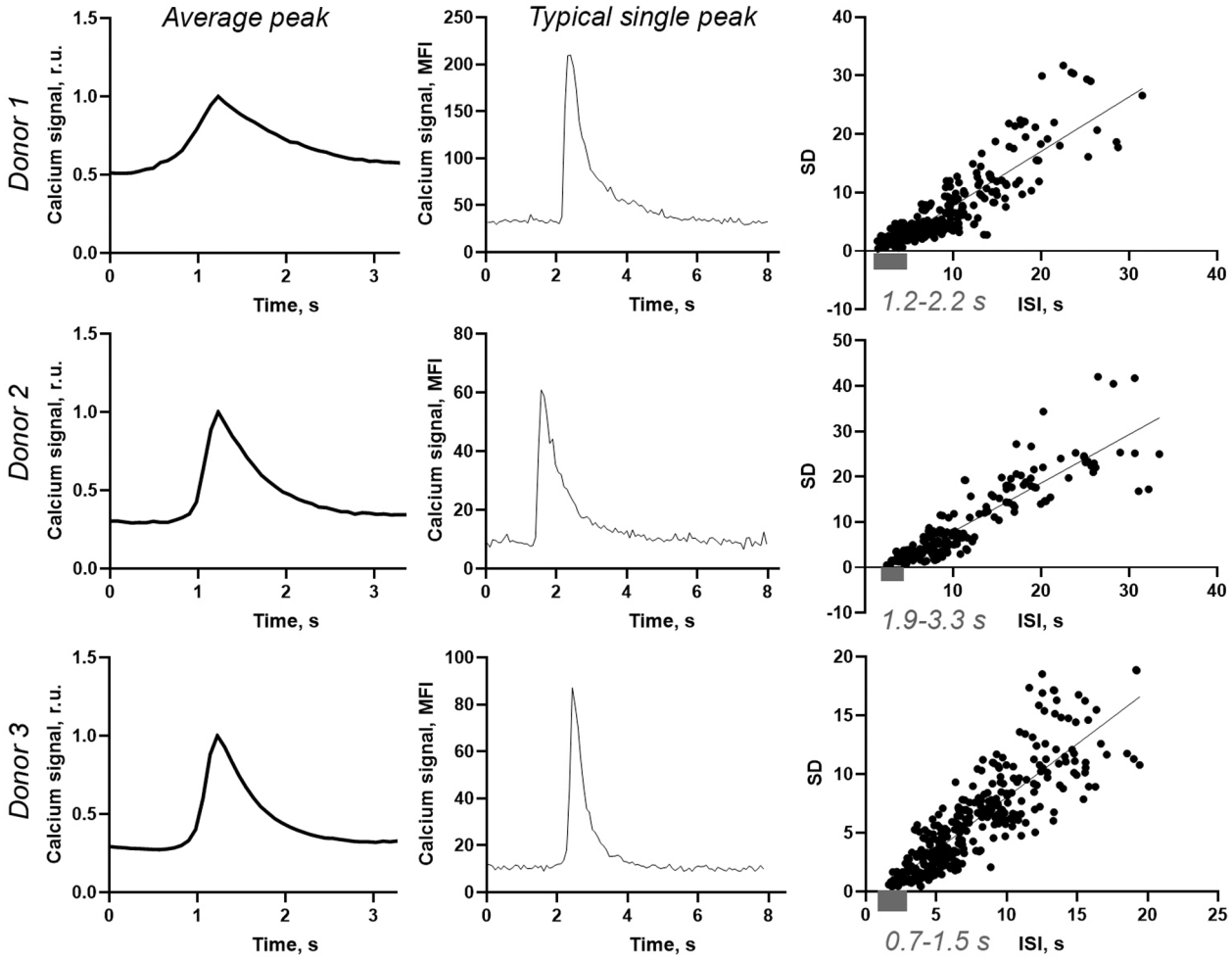

Figure 3. Properties of calcium oscillations of platelets from three healthy donors. Each row of the panels corresponds to one donor. The average calcium peak (left), the characteristic shape of a single peak (center) and the dependence of the standard deviation of the peak intervals from the average for the peak intervals (right) are presented.

model parameters (DTS calcium concentrations, SERCA and IP_3R catalytic rate constants, and calcium buffering parameters) to describe experimental data — two characteristic calcium spikes distances by a minimum ISI (Fig. 4a–c). The accuracy (RMS) of the parameter estimation was 0.12–0.18 (Table S3). Additionally, validation was performed on the ability to predict a single peak (Fig. 3, Fig. S1), the accuracy of the description of a single peak was 0.2–0.23 (Table S4). In all cases, the deviation of the experimental data from the model was less than 1% of the average value. As a result, the stimulus-response curves characteristic of each donor were calculated (Fig. 4d).

The analysis of the constructed models has shown that, although the parameters of calcium signaling of healthy donors vary significantly (Table 1, Fig. 3), characteristic single calcium peaks and stimulus-response curves turn out to be qualitatively similar (Fig. 4d). These results can be explained by the occurrence of internal compensatory mechanisms during platelet formation. Although the proteomic data show great heterogeneity for each specific protein (Fig. 4e), there is a correlation between the total number of SERCA calcium pumps and the total number of IP_3R calcium channels (Fig. 4f).

DISCUSSION

Although personalization holds immense potential to enhance treatment efficacy across various diseases, its practical application remains limited. Considering individual patient characteristics — often specific genomic polymorphisms that mildly influence drug metabolism or signal transduction — rarely produces results that justify the efforts invested. However, personalized modeling of a patient's physiological systems has the potential to change this trend.

Attempts to personalize the platelet response were previously undertaken by the Scott Diamond's team based on neural networks [36], which were then integrated with the thrombosis model [37]. However, neural networks do not allow us to identify the mechanisms of problems and propose fundamentally new approaches to treatment. Mechanistic models

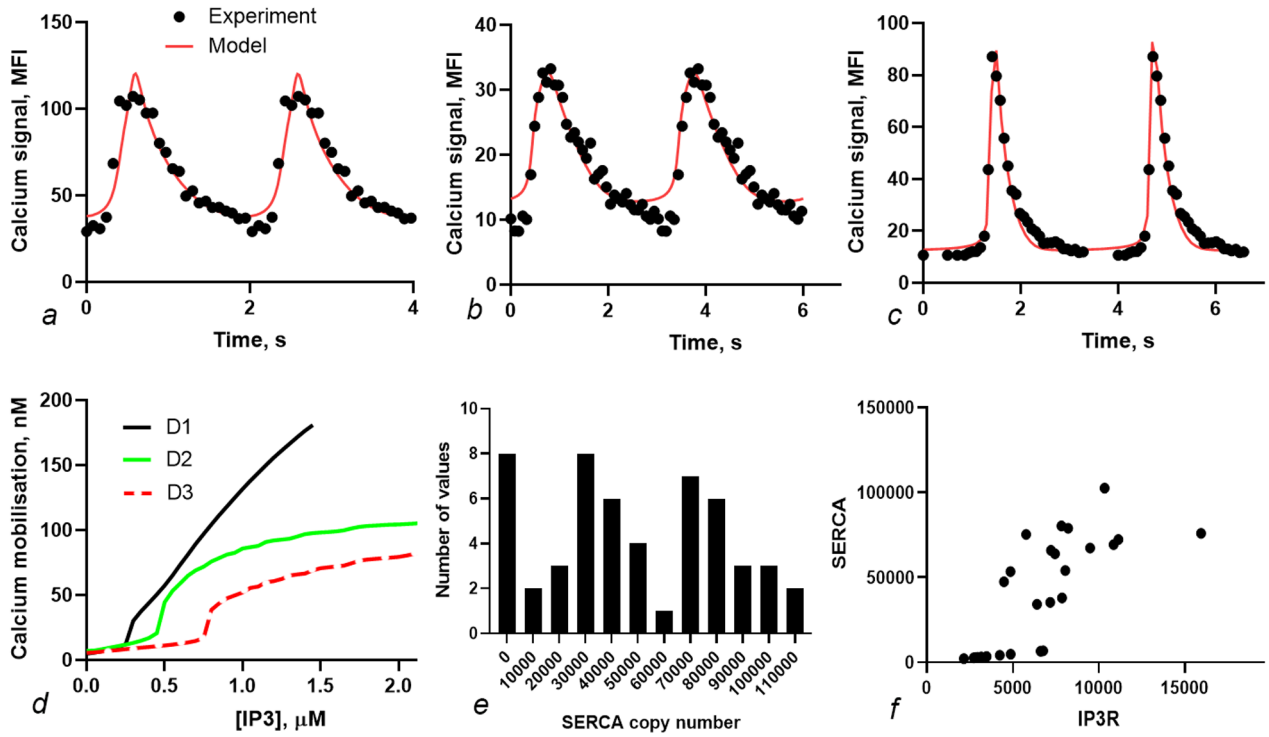

Figure 4. Parameters of calcium signaling. (**a-c**) Approximation of experimental data for three healthy donors (Table 1). (**d**) Signal-response dependence for the obtained personal models, the integral concentration of calcium is represented along the ordinate axis. (**e**) A histogram of the SERCA2a distribution in the proteomics data of 15 healthy donors from the work [20]. (**f**) The dependence of the total amount of SERCA on the total amount of IP_3R [20].

in this regard seem to be much more promising, especially as the details of the system structure become clearer. Although there are no such models for platelets, there is a vivid example of the research of the Brummel-Ziedins group for blood coagulation: the approach they developed to personalize the dynamics of thrombin generation based on blood plasma composition [38] has successfully manifested itself in a wide range of issues from clotting problems in rheumatoid arthritis [39] to the prediction of thrombosis in thrombophilia [40].

In this study, we took a step toward personalized modeling for platelets by focusing on the dynamics of calcium responses, a central element in the platelet signaling. Due to the complexity of this signaling system, we used both functional tests and proteomics data to personalize the models. Alongside addressing the core personalization task, we identified key features of the platelet calcium response and its defining parameters, emphasizing the critical role of balancing activators and inhibitors in platelet signaling. This balance allows platelets to produce consistent and standardized responses to stimulation.

In this paper, we confirmed the results obtained earlier [21] on the calcium peak asymmetry in a single platelet (Fig. 3). At the same time, in contrast to the average peak, which has a linear dynamics of rise and fall in concentration, the characteristic single peak has a sharp rise and exponential decline. To describe the characteristic rate of decrease in calcium concentration, buffering of calcium ions has been introduced into the model, due to the fact that each calcium-binding protein removes calcium ions from the pool capable of moving between ER and cytosol [41]. A similar approach was proposed by Wagner and Keizer [28]. Buffering of calcium makes it possible to increase the width of the calcium peak, which is confirmed by an increase in the calcium response to stimulation in the first donor (Fig. 3). The rapid increase in calcium concentration can be explained by the local mutual activation of IP_3Rs located close to each other in the platelet [27, 42]. Since the donors under consideration differed not only in the number of receptors, but also in the volume of ER, it makes sense to compare the IP_3R activity: 51 μM/s, 35 μM/s, and 20 μM/s for the first, second, and third donors, respectively. Thus, a sharp rise in calcium in single peaks correlates with IP_3R activity.

The ratio of IP_3R and SERCA activities will affect the frequency and amplitude of the oscillations, which, in turn, determine the platelet responses. For example, we have previously shown that mitochondria [5] and integrins [9] are “integrators” of calcium oscillations in the platelet [18]: for each peak of calcium, a signal is “read” depending on its width, and in the absence of a peak, relaxation occurs. Similar mechanisms have been analyzed in detail for calcium signaling in other cells [28]. Thus, for a balanced

response, it is not so much the constant activity of enzymes that must be maintained, as the balance of "activators" and "inhibitors", which is confirmed by the analysis (Fig. 4f).

The limitation of this study is that it considers a small (albeit central) part of platelet signaling, without taking into account the upstream signaling pathways from membrane receptors and downstream pathways leading to functional responses. Despite the fact that the computer model of this study is mechanistic, its basic scheme includes a number of assumptions and simplifications related to the mechanisms of operation of individual reactions and molecules. The architecture of the model itself also includes a number of fundamental assumptions: the neglect of diffusion, the lack of consideration of platelet heterogeneity, deterministic simulations. Regardless of the improvement of the model and its personalization algorithms, their validation on a large number of samples of healthy volunteers, patients, as well as the study of pharmacological effects should be an important next step that will provide information about the principles of regulation of platelet signaling and possible approaches to its correction.

Further development in this area should be the expansion of the personalized model to the entire set of signaling pathways and functional platelet responses, incorporation of drugs into the model and the personalization of drug responses, and finally, connecting a thrombotic status and clinically significant outcomes. Despite the complexity and scale of such a task, addressing this need is critical. Thrombosis and bleeding are collectively responsible for substantial proportion of mortality in the modern world, and all existing anti-thrombosis drugs cause bleeding. Since the hemostatic system functions similarly in both hemostasis and thrombotic, the likelihood of discovering a single "magic bullet" to treat thrombosis without affecting hemostasis is minimal. However, the personalization of therapy, guided by a comprehensive mechanistic model, holds the potential to shift the probabilities in a favorable direction for each individual patient, enabling more effective and safer treatment strategies.

FUNDING

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COMPLIANCE WITH ETHICAL STANDARDS

In this study, the theoretical processing of previously published experimental data for healthy pediatric donors has been carried out [20].

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

Supplementary materials are available in the electronic version at the journal site (pbmc.ibmc.msk.ru).

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ПЕРСОНАЛИЗАЦИЯ ВЫЧИСЛИТЕЛЬНОЙ СИСТЕМНО-БИОЛОГИЧЕСКОЙ МОДЕЛИ КАЛЬЦИЕВОЙ СИГНАЛИЗАЦИИ ТРОМБОЦИТОВ

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Безъядерные клетки крови — тромбоциты — являются основой для образования тромбов в сосудах человека, а антитромбоцитарная терапия относится к наиболее распространённым, так как применяется после ишемических событий и для их профилактики. Однако, в силу ограниченной эффективности и рисков кровотечений, существует потребность в её персонализации. Ранее мы разработали серию вычислительных моделей для описания внутриклеточной сигнализации тромбоцитов и систему экспериментальных методов, позволяющих охарактеризовать тромбоциты конкретного пациента. Также было проведено исследование по протеомике тромбоцитов. Целью настоящего исследования была персонализация центрального модуля внутриклеточной сигнализации тромбоцита, отвечающего за формироования осцилляций концентрации кальция в ответ на активацию. Модель представляет собой систему из 26 обыкновенных дифференциальных уравнений. Для персонализации модели используются данные протеомики и проводится подбор неизвестных параметров модели по экспериментальным данным о форме и частоте осцилляций кальция в одиночных тромбоцитах конкретного пациента. В результате исследования показано, что ключевыми персонализируемыми параметрами осцилляторного ответа тромбоцита являются степень асимметрии одиночного спайка кальция и максимальная частота осцилляций. В работе были рассмотрены три здоровых педиатрических донора разного возраста. На основе моделей были получены персональные кривые кальциевого ответа тромбоцитов на активацию. Анализ моделей показал, что в то время как наблюдается большая гетерогенность отдельных показателей внутриклеточной сигнализации, таких как активность кальциевых помп (SERCA) и рецепторов к инозитолтрифосфату (IP_3R), эти показатели компенсируют друг друга у каждого донора. Это наблюдение подтверждается анализом данных протеомики 15 здоровых доноров, согласно которым наблюдается корреляция суммарного количества SERCA и IP_3R. Таким образом, в настоящей работе показано несколько новых особенностей кальциевой сигнализации тромбоцитов человека и предложен алгоритм персонализации её модели.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: тромбоциты; кальциевая сигнализация; рецептор к инозитол-3-фосфату; компьютерное моделирование

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