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In silico modelling of hemostatic response: challenges and perspectives

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In vertebrates' hemostasis represents a tightly controlled process represented with interwound system of various elements, including cellular and plasma-based reactions. Despite the enormous clinical significance of the principles governing hemostatic response and decades of ongoing research, current understanding of the basic mechanisms that regulate the dynamics of both hemostatic and pathological thrombus formation is very limited. Today in silico approaches became indispensable for investigation of the multiple aspects of the problem that are hardly tackled with the experimental methods.

This overview is aimed to highlight the basic problems in the field and the challenges faced by the current computational models while trying to address multiple burning questions.

To illustrate the principles exploited by the state-of-the art models we give a short overview of the recently described approaches and further provide our view on the existing gaps of knowledge and future instruments required to accomplish these goals.

KED peptide prevents synaptic contacts elimination of hippocampus neurons in an in vivo Alzheimer's disease model

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Background: Cognitive impairment in Alzheimer's disease (AD) correlates with the synaptic contacts elimination. Morphologically, this is manifested in the number decrease of dendritic spines in hippocampal neurons. KED (Lys-Glu-Asp) and EDR (Glu-Asp-Arg) peptides increased the number of dendritic spines in an in vitro AD model.

Aims: The aim of this work is to assess the effect of KED and EDR peptides on the number of dendritic spines in hippocampal neurons in the in vivo AD model.

Methods: For AD model was used a transgenic 5xFAD-M mice cross-line. Animals of this line (3-5 months) were daily injected with KED and EDR peptides (400 μg/kg) or saline (control 2). M line mice, which were injected with saline, served as control 1 (normal).
The density (DS) and the relative number of mushroom (MS) and thin (TS) dendritic spines of CA1 neurons in the hippocampus were estimated on fixed brain slices using confocal microscopy and micrographs analysis in the NeuronStudio software. Statistical analysis of the data was performed using the Statistica 12 software. The animal study was followed the principles of the European convention (Strasbourg, 1986) and the Declaration of International medical association about the humane treatment of animals (Helsinki, 1996).

Results: Normally, DS, MS, and TS were 12.89 ± 0.32 c.u., 44.57 ± 1.11%, and 40.61 ± 1.26%, respectively. In control 2, DS and MS decreased statistically significantly by 15% ($p = 0.011$) to 11.31 ± 0.36 c.u. and by 20% ($p = 0.00002$) to 35.61 ± 1.64%, respectively, compared with the norm. TS increased by 19% ($p = 0.00003$) to 50.15 ± 1.81% compared to the norm.

KED peptide in 5xFAD-M mice statistically significantly increased MS by 16% ($p = 0.024$) to 44.89 ± 1.65% and decreased TS by 13% ($p = 0.008$) to 43.84 ± 1.83% compared to control 2. After KED peptide injection MS and TS did not differ significantly from the norm ($p = 0.157$ and $p = 0.156$, respectively).

EDR peptide administration to 5xFAD-M mice promoted a statistically significant increase in DS by 11% ($p = 0.039$) to 12.64 ± 0.31 c.u. and a decrease in TS by 10% ($p = 0.024$) to 44.84 ± 1.65% compared with control 2.

Conclusions: KED peptide systematic administration prevents the elimination of the most functional synaptic contacts of the mushroom type in the CA1 hippocampus neurons in 5xFAD-M mice. It should be emphasized that the KED peptide normalizes the balance of thin and mushroom spines, which is necessary for memory restoration in AD.

Numerical and qualitative investigation of the mathematical model of blood coagulation with membrane reactions

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Background: Mathematical modeling is extensively used for understanding various aspects of blood clotting. Yet mathematical models remain mostly qualitative and very often contain some non-physiological assumptions.

Aims: The aim of quantitative correspondence of the mathematical models and the experimental results require some corrections in model equations. Set of the model's equations are modified based on systematic bifurcation analysis and qualitative properties. On the other hand, the qualitative correspondence could be achieved by the multi-parametric fitting of the numerical modeling data vs experimental results.

Methods: The set of equations consist of 46 ODE. To solve the ODE system, the one-step Rosenbrock's method with complex coefficients (CROS) was used. By the parameter sensitivity function, we mean the proportionality coefficient between the relative change in the coefficient and the resulting relative change in the function. The sensitivity function is constructed numerically. To achieve the best possible quantitative correspondence, the authors apply the modification of Broyden's method for non-linear optimization. The results obtained clearly demonstrate that the quantitative correspondence requires some changes in the mathematical model.

Results: Introduction of fXI related reaction is proven to be necessary for the mathematical model to avoid non-physiological effect of initial non-zero fIIa concentration. This is a significant qualitative improvement of model as there are no experimental evidence of fIIa existence in blood outside of clotting reaction zones.
Broyden's method is shown to be an efficient tool with automatized capabilities for multiparametric fitting of the experimental data with numerical results.
It can be seen that sensitivity to all test constants occurs when a sufficiently large number of activated platelets and activated V factor are formed in the system. And sensitivity virtually disappears or stabilizes during the period of the fastest increase in thrombin concentration activated.

The effect of the V factor is from platelet activation to the start of the main cascade (about 100 to 400 seconds). In this case, reactions involving factor V play a greater role in the dynamics of the process than the lipid composition of the membrane (sensitivity is higher by about 2.5 orders of magnitude).

Conclusions: The fXI modified clotting model demonstrates qualitative correspondence to the experimental data on fIIa kinetics but also a significant quantitative mismatch. Authors tend to attribute the quantitative discrepancies to the model properties which manifested themselves after removal of masking effect of initial non-zero fIIa concentration. In particular authors suspect that fII activation reactions in the bulk and on platelet membranes are imbalanced after comparing with the experiment.