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A STOCHASTIC PETRI NET MODEL TO SIMULATE THE INTRINSIC VARIABILITY OF TISSUE FACTOR INDUCED COAGULATION CASCADE

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ABSTRACT

This paper introduce a Stochastic Petri Net (SPN) based model to capture the variability of biological systems. The coagulation cascade, a tangled biochemical networks, has been widely analyzed in literature mostly with ordinary differential equations, outlining the general behavior but without pointing out its intrinsic variability. Moreover, the computer simulation allows the assessment of the reactions over a broad range of conditions providing a useful tool for the development and management of several observational studies, potentially customizable for each patient. We describe the SPN model for the Tissue Factor (TF) induced coagulation cascade and its simulation using Tau-Leaping SSA. We simulate different settings representing the cases of "healthy" and "unhealthy" subjects, analyzing their average behavior, their inter- and intra-variability.

1 INTRODUCTION

Using the Petri Nets extension, Stochastic Petri Nets (SPNs), we can describe biological random aspects (Srivastava, Peterson and Bentley, 2001), and obtain a friendly graphical representation of Coagulation Cascade, which has recently attracted strong interest for its potential to augment bioclinical knowledge in several therapeutic domains (Chatterjee et al., 2010; Wajima, Isbister and Duffull, 2009). The characteristic variability of the coagulation pathway has been considered in literature by a few works using different techniques (Filipovic, Kojic and Tsuda 2008) (Lo et al., 2005). However, none of these stochastic approaches allows an analysis matched with existing clinical tests, in particular the "Prothrombin Time" (PT) test. We developed a model based on a Petri Net modeling framework of TF pathway, which represents a new stochastic bioclinical approach of modelization of the extrinsic pathway to have model applicable to clinical analysis.

2 PETRI NET MODEL AND BIOCHEMICAL PATHWAY

The starting point in building the model is to define the initial marking and reaction rate constants, which we obtained from databases as Brenda, model repositories as BioModel Database,integrated with data found in PubMed. The initial marking (M_0) represents in our model the average value of the observed physiological range. The reaction rates have been tuned with a trial and error approach (based on enzyme kinetic assumptions) to replicate the thrombin generation time given by the bioclinical PT test (Khanin et al., 1999), and reproduce a titration curve of the thrombin formation (Butenas, van't Veer and

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Mann,1999). In M_0, only 11 places have a non-zero number of tokens, which ranges from 75 to $3{,}01 \cdot 10^8$ molecules with a considered plasma volume of $1 \cdot 10^{-10}$ liters.

3 STOCHASTIC SIMULATION

Stochastic Simulation Algorithm (SSA) is usually performed by the "Direct Method", proposed by Gillespie, which is computationally prohibitive even for mid size models ; one variant , "tau -leaping method" (Gillespie, 2001) is much faster and allows to simulate different scenarios .

4 EXPERIMENTAL RESULTS

We can consider the phenomenon of variability of this system from two points of view regarding the results of simulations: Inter-variability, different subjects with the same initial marking, that lead them to have different patterns of coagulation; Intra-variability: a single subject with an average initial marking, who can show different trends because of the intrinsic variability. In both cases, performing several simulations we can observe how the variability of biological system is reproducible by stochastic simulation. This approach allow us to evaluate whether the sample paths generated by simulation follows the real behavior of the system in normal and stressed conditions, allowing the validation of our models.

5 CONCLUSIONS

We proved that a stochastic approach allows to detect important features that deterministic models cannot discover: first, there are molecule types which appears in a very low amount (up to 10 molecules), which only the stochastic method allows to simulate without mathematical artifacts; second, we shown that an increase in the quantity of Tissue Factor and/or VIIaTF complex (the trigger molecules) reduces the degree of variation of the system, which is confirmed by clinical evidence where the biological variability is lower in of patients with pro-thrombotic conditions, and higher in patients with pro-haemorragic phenotypes; finally, only the stochastic simulation identified the high fluctuability in the system during critical phases, which will allow to analyze deeper how much the particles reacts when the system is at the peak of its activity.

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