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# Webinars

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## Mechanistic Insights into the Russell's Viper Venom Factor V Activating Enzyme: A QM/MM Study

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Snakebite envenoming is a major health issue, causing approximately 50,000 deaths annually in the Indian subcontinent. The Russell's viper (*Daboia russelii*) is particularly significant, as its venom contains RVV-V, a serine protease that activates coagulation factor V (FV) disrupting the haemostatic system, leading to severe coagulopathy and potentially death. Despite their importance, the mechanisms of these venom enzymes remain underexplored compared to human serine proteases.

In this study, we examine the mechanism of FV hydrolysis by RVV-V using umbrella sampling molecular dynamics simulations with the B3LYP/AMBER level. Our findings indicate a stepwise mechanism in which the acylation step is rate-limiting, with a calculated activation free energy of 24.8 kcal·mol$^{-1}$. The acylation step proceeds through a single, asynchronous transition state without formation of a stable tetrahedral intermediate, consistent with a concerted pathway. In contrast, the subsequent deacylation step follows a two-stage reaction mechanism, involving two transition states.

Comparison between the computed rate-limiting transition state and crystallographic inhibitor-bound complexes shows strong structural agreement. These findings reinforce the validity of the proposed mechanism and establish a foundation for the rational design of transition-state analogue inhibitors that target snakebite envenoming, with potential relevance for broader coagulation disorders.

**Short Bio**

Juliana Amorim holds a BSc in Biology and an MSc in Biochemistry and is currently a PhD student on the Doctoral Programme in Chemistry. Her research focuses on computational biochemistry and molecular modelling, particularly in enzymatic mechanisms, molecular dynamics, and drug discovery. Her main focus is on understanding the enzymatic mechanisms of snake venom toxins using quantum mechanics/molecular mechanics (QM/MM) approaches to support the development of universal, effective, and affordable therapeutics for snakebite envenoming.

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