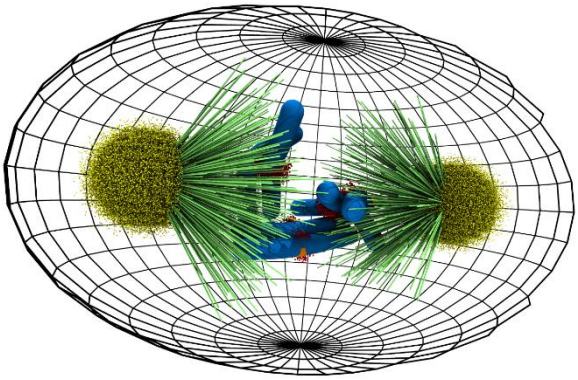
Title: CellDynaMo – Stochastic Reaction-Diffusion-Dynamics Model of Biological Systems: Application to Search-and-Capture Process of Mitotic Spindle Assembly

Valeri Barsegov, University of Massachusetts Lowell

Abstract: We introduce a Stochastic Reaction-Diffusion-Dynamics Model (SRDDM) for GPU-accelerated simulations of mechanochemical processes in macrosopic biological systems with high spatial and temporal resolution. The SRDDM model is mapped into the CellDynaMo package, which couples the spatially inhomogeneous reaction-diffusion master equation to account for biochemical reactions and molecular transport with the Langevin Dynamics (LD) framework to describe relevant dynamic mechanical processes. This computational infrastructure allows the simulation of hours of the dynamics of large and complex biological in reasonable wall-clock time. We apply the model to test performance of the Search-and-Capture model of mitotic spindle assembly by simulating, in three spatial dimensions, dynamic instability of elastic microtubules anchored in two centrosomes, movement and deformations of geometrically realistic centromeres with flexible kinetochores and chromosome arms. Furthermore, the SRDDM model describes the mechanics and kinetics of Ndc80 linkers mediating transient attachments of microtubules to the chromosomal kinetochores. The rates of these attachments and detachments depend upon phosphorylation states of the Ndc80 linkers, which are regulated in the model by explicitly accounting for the reactions of Aurora A and B kinase enzymes, which undergo restricted diffusion. We find that there is an optimal rate of microtubule-kinetochore detachments which maximizes the accuracy of the chromosome connections, that adding chromosome arms to kinetochores improve the accuracy by slowing down chromosome movements, that Aurora A and kinetochore deformations have a small positive effect on the attachment accuracy, and that thermal fluctuations of the microtubules increase the rates of kinetochore capture and also improve the accuracy of spindle assembly. The SRDDM model implemented in the CellDynaMo package can now be used to model a large number of physico-chemical processes that occur in complex biological systems. Selected model applications to the blood clot contraction and forced rupture of fibrin network are described.



Biosketch: Dr. Valeri Barsegov obtained his Bachelors in Chemistry from the Moscow State University, Russia, in 1994. He entered graduate school in 1994 and received his PhD degree in 2000 from the University of Texas at Austin, where he worked under the supervision of Prof. Peter Rossky (Department of Chemistry) and Prof. Ilya Prigogine (Department of Physics and Astronomy). Dr. Barsegov received the postdoctoral training at the University of Rochester in 2001-2003, and at the Institute for Physical Science and Technology, University of Maryland, College Park in 2003-2006. Dr. Barsegov joined the Department of Chemistry, University of Massachusetts Lowell in 2005. Prof. Valeri Barsegov develops theoretical and computational approaches to explore complex biological systems. His research has contributed to the emergence of new fields of research: (i) biomechanics of hemostasis/thrombosis [*Acta Biomaterialia*, **136**, 327 (2021); *Acta Biomaterialia*, **131**, 355 (2021); *Proc. Natl. Acad. Sci* **115**, 8575 (2018); *Structure* **26**, 857 (2018); *J Am Chem Soc* **139**, 16168 (2017); *Structure* **24**, 1907 (2016); *J Am Chem Soc* **134**, 20396 (2012)]; (ii) physical virology [*Acta Biomaterialia*, **122**, 263-277 (2021); *Biomacromol* **17**, 2522 (2016); *PLoS Comp Biol* **12**, e1004729 (2016) *J Am Chem Soc* **136**, 17036 (2014); *Biophys J* **105**, 1893 (2013)]; (iii) high-performance computing [*Proteins* **78**, 2984 (2010); *J Phys Chem B* **115**, 5278 (2011); *J Comp Chem* **37**, 1537 (2016)]; and (iv) computational cell biology [*PLoS Comp Biol* **18**, e1010165 (2022)].