Monitoring cascades of events in living cells requires non-destructive methods to follow biological processes. Fluorescent imaging exploiting the FRET effect between spectral variants of the Green Fluorescent Protein has become a prevailing tool in following the spatio-temporal localization of molecular events. Surprisingly, genetically encoded FRET sensors are regularly used even if the detailed molecular basis ruling its functioning are not completely understood. In fact, the design of fluorescent probes is commonly undertaken as a trial-and-error (often frustrating) procedure. However, the use of structural information in combination with molecular simulation techniques can help to overcome this limitation resulting in a significant reduction of the time and effort needed to design molecular markers. Moreover, the use of simplified or Coarse Grained (CG) molecular representations help to extend the sizes and times scales accessible to computer simulations, reaching biologically relevant dimensions.

In this presentation we will review the recent development of the SIRAH CG force field (www.sirahff.com) for biomolecular systems and a particular application to the design of FRET sensors to detect the second messenger cAMP in living cells, which makes use of the allosteric mechanism of the regulatory subunit of the Protein Kinase A.