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From hepatocyte polarization to canalicular network formation: a multiscale approach

The generation and maintenance of hepatocyte polarity is crucial for the proper functioning of the liver, and is important in development, as well as liver regeneration. It is well-known that the complex polarity of hepatocytes is characterized by the existence of multiple basolateral and apical/canalicular poles per cell. Yet, it remains unclear what molecular and cellular interactions regulate the generation of segregated membrane domains, and how this affects the morphology of the hepatic epithelium and the formation of bile canulicular network.
To investigate the feedback between the molecular and cellular interactions, we have developed a multiscale modeling environment called Morpheus. This modeling and simulation framework facilitates the integrative modeling of multiscale cellular systems, and includes solvers for discrete and continuous models, a XML-based modeling language, and a graphical modeling interface.
To study the generation and consequences of hepatocyte polarity, we established a hybrid model consists of two modules. The molecular interactions between Rho GTPases and phosphoinositides (PIPs) are modeled using a reaction-diffusion (PDE) formalism. Anisotropic adhesion and bile secretion between cells are represented in a cellular Potts model. The integration of the modules is based on cell-cell and cell-matrix signals that trigger polarization of membrane proteins, and the downstream effects of membrane domains on the formation of tight junctions and bile secretion at the apical/canalicular domain. Our results are compared to quantitative data on the polarity and tissue morphology of murine hepatocytes in *in vitro* sandwich cultures.