**Development of a multiscale skin barrier model for *de novo,* *in silico* prediction.**

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We developed a multiscale, many-cell skin barrier model. Our strategy was the integration of four distinct models, mostly skin specific, that have been previously validated and described in the literature. We model cells as discrete elements within a continuous environment. The foundation is a three-dimensional, agent-based model of barrier formation and epidermal homeostasis. For transport of molecular species in the extracellular space, we have employed a continuous, multi-compartment skin penetration model. A continuum representation is also employed to capture hydration and water transport modulating cell swelling and TransEpidermal Water Loss (TEWL; a clinical measure of barrier). Finally, we apply a system of ordinary differential equations in each basal cells to capture intracellular biomolecular processes related to cell cycle control.

This integration is done on the high-performance computing (HPC) platform Biocellion. Beyond the general integration of continuum and agent based models, the platform allowed complex geometries for initialization (e.g. rete pegs), an adaptive mesh to modulate extracellular grid resolution, and mechanical interactions between non-spherical elements (e.g. coenocytes). Although sometimes implemented in other platforms, Biocellion provided the level of detail and flexibility necessary to maintain the integrity of the underlying source models. In addition, the unprecedented computational power allows the domain size to easily reach mm length scales and time scales at days without the need for computer clusters, of course length and time could be scaled up on HPC systems. Because we model individual cells, reactions and transport at micron length scales, and because we simulate whole tissue scales of mm and days, this model is a true three-dimensional, multiscale representation of a dynamic skin barrier.

To demonstrate utility, we investigated the potential for *de novo, in silico* prediction of barrier response to external stimuli. For this initial case-study, we chose a strong chemical stimuli, a CDK1/CDC2 inhibitor. Because we employed a molecular-based cell cycle model that included CDC2, we were able to directly simulate the effect on the molecular cell cycle control program using only the IC50 values. Intracellular concentration was determined by local extracellular concentration and cell permeability, via a well-accepted i*n vitro* assay. Finally, local concentrations are dynamical computed by the skin penetration model with diffusion coefficients derived form reported chemical properties. Thus simulations of inhibitor response can be parameterized without any training, optimization or complex *in vivo/ex vivo* studies. The final result showed that the inhibitor leads to the slow disappearance of the viable skin layers and then the stratum corneum. When the barrier is compromised, penetration of the inhibitor notable accelerates and the remaining epidermis quickly degrades. This exemplifies feedback between the agent-based morphological and continuum-based transport models. Throughout the simulation, an increase of TEWL is observed, connecting the computational model to clinically relevant measures of human barrier function.