# Interactive Platform for Virtual Tissue Modeling

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We have created a computational research platform for high fidelity modeling of tissue development, organization, and function. The resulting 3-D virtual tissue models are grounded in cell biology: cells, genes, cellular pathways and processes, signaling and gene regulatory networks, and physical parameters are represented in software that grows multicellular virtual tissues with many features of living systems [1].

The platform includes primitives for signaling, adhesion, extracellular matrix (ECM), transport and surface binding, secretion, cell cycle, molecule turnover, apoptosis, and gene expression. Higher order tissue properties are not specified, but instead emerge from transactions carried out by molecules within and between cells according to rules specified in the physics of the model, resulting in actions such as cell division, growth, or death. Cell types arise by controlled gene expression.

Cell-based *in silico* modeling is an important part of any comprehensive approach [2] to identify target pathways and predict effects of mutations, drug treatments, or physical manipulations on tissue organization and function, *in vivo* or in culture. Our technology provides capabilities that conventional wet-bench approaches do not have: it is possible to measure, monitor, or manipulate the internal state of any cell without disrupting the tissue. The models also serve as high-throughput hypothesis testers for refinement of wet-bench studies.
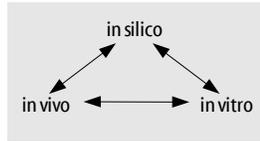
Starting from a single cell, an epithelial model developed on this system (Fig. 1) exhibits dynamic turnover through death and sloughing of cells at the apical surface coupled with replenishment from pockets of basal stem cells. As development proceeds, steady-state, homeostatic balance is reached between decay and synthesis of molecules, distorting forces and anchorage, cell death and replacement, and so forth. Microenvironments are created with conditions suitable for controlling cell behavior (e.g., curtailing growth by
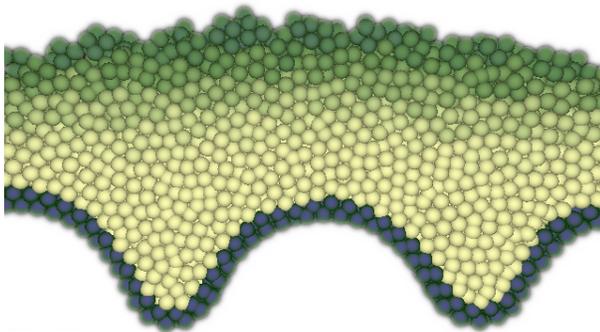

Figure 1: Cross-section of a virtual epidermis grown from a single cell on a surface coated with ECM (blue). In basal cells suppression of lipid synthesis is highest (yellow), decreasing (shades of green) as cells are displaced toward the apical surface.
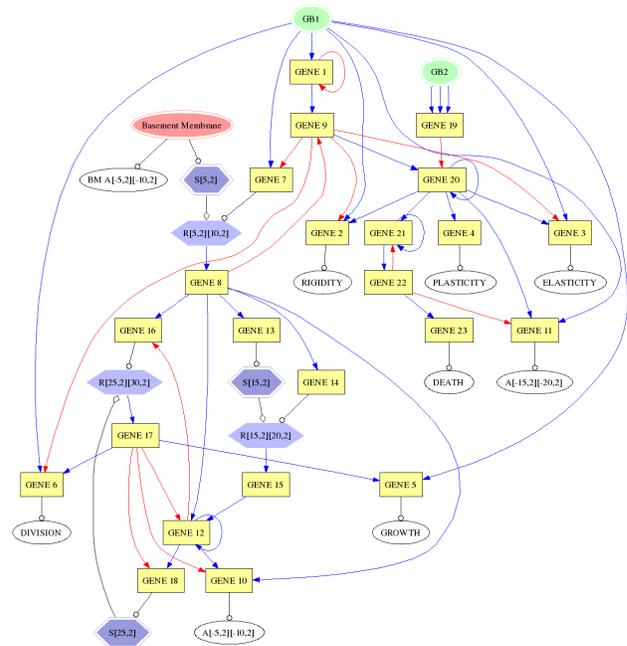

Figure 2: Signaling and gene regulatory network for a virtual epidermis

signaling repression). Parameters that affect tissue architecture and physiology include signals from neighbors; types of ECM; attachment, anchorage and surface molecules; cell shape; soluble molecules and secreted gene products. The resulting multicellular virtual tissues are stable yet dynamic: responsive to stimuli, injury, or mutation.

To investigate the underlying mechanisms that support tissue stability and response to perturbation, our software enables analysis of signaling and gene expression. Networks of interactions may be examined on a cell-by-cell basis or summarized for the tissue as a whole (Fig. 2) by pausing the model at any time during development or stasis.

From its remote access interface, this platform enables researchers to investigate the rules cells follow to become and remain healthy tissue, and explore the diseased states that result when these rules are violated [3]. A researcher can easily introduce targeted mutations, gene knockouts, or alterations of path connectivity, and monitor their effects on subsequent growth, differentiation, organization and function. For instance, removing the gene encoding receptors that are part of an inhibitory feedback loop controlling cell division, existing receptor molecules decay in the mutated cell and are not replaced, restraint on division subsides, and the tissue becomes dominated by cancerous cells.

References:
1. Noble, D. (2003) *Biochem. Soc. Transactions 31*:156-158.
2. Kirschner, M. (2005) *Cell 121*:503-504.
3. Bissell, M. et al. (2003) *Curr. Opinion Cell Biol. 15*:753-762.