

A Layered Cell Model for Morphoproteomics

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1. Morphoproteomics

The Morphoproteomics paradigm in cancer research views tumorigenesis as a consequence of multifactorial interactions of genetics, cell cycle, signaling pathways, intracellular venues of specific protein-protein interactions, and others (Figure 1) [1]. In this algorithmic and personalized approach, development of cancer therapies requires integrated understanding of heterogeneous knowledge. For example, a tumor-suppressing drug may have greatest benefit if administered when (most of) the tumor cells are in a particular cell cycle phase. Systems biology tools to support morphoproteomics must, therefore, reflect the complete complexity of biological cells.

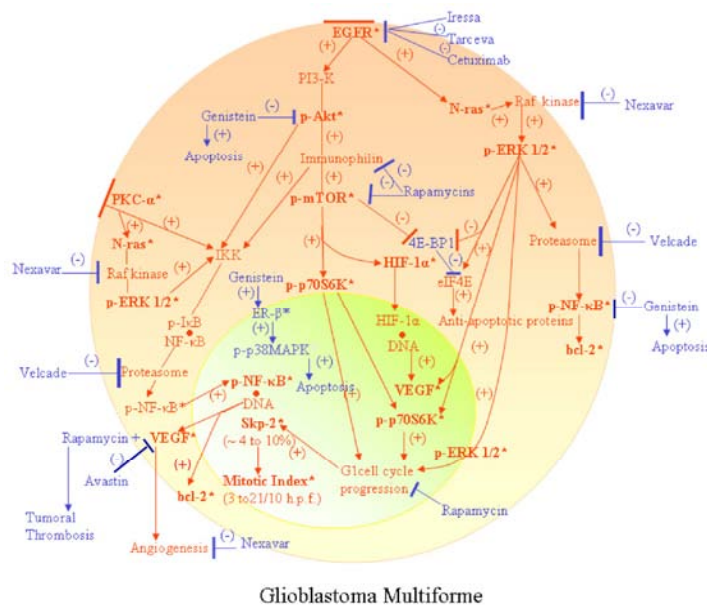


Figure 1: Morphoproteomic representation of Glioblastoma multiforme.

Biological cells are organic machines with complex morphological structure in which intricate biochemical processes (metabolic/ signaling pathways) containing hundreds of proteins interact in multiple ways. They also exhibit dynamic behavior over time. Creating complete executable software descriptions of the whole cell is a formidable task [2]. We propose a framework called the Layered Cell Model (LCM) to facilitate such development.

2. Taming Complexity

Two important strategies for taming complexity are *Abstraction*: capturing the essential attributes of domain knowledge, and *Modularity*: decomposing a complex system into manageable modules “solved” by domain specialists [3, 4]. Module assembly is accomplished by *Application Programming Interfaces* specifying syntax/semantics of module input/output.

3. Layered Cell Model

In the LCM (Figure 2), each layer contains relevant implementations of mathematical algorithms, software, databases, protocols and other constructs, tagged with temporal information. Layers are defined chiefly by commonality of knowledge.

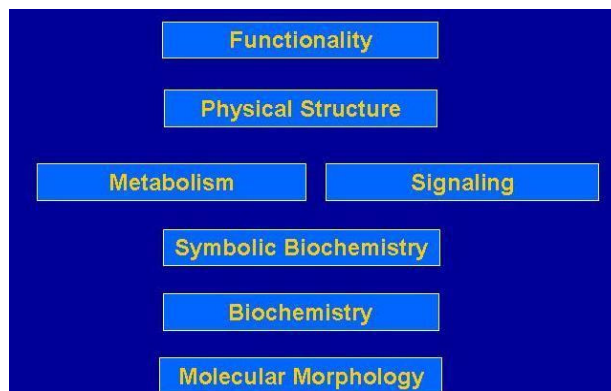


Figure 2: Multi-layer reference framework for *in silico* cell modeling

- 1. Molecular Morphology:** Molecular modeling, i.e., the structure and form of bio-molecules. Examples: Software and mathematical models representing protein confirmation, protein folding [5], molecular dynamics.
- 2. Biochemistry:** Thermodynamic processes (rate constants, reaction kinetics) of intracellular biochemistry. Example: Michaelis-Menten equation.
- 3. Symbolic Biochemistry:** Symbolic models of biochemical assemblies. Examples: the genome as a sequence of base-pairs, proteins as sequences of amino acids, BLAST [6].
- 4. Metabolism:** Symbolic representations of pathways by which the cell converts nutrients into energy. Examples: BioCyc[7], e-cell [8].
- 5. Signal Transduction:** Symbolic representations of pathways of inter-cellular and intra-cellular communications. Examples: Pi Calculus, Pathway Logic [9].
- 6. Physical Structure:** Representations of cell morphology as an assembly of 3-D structures (cytoskeleton, nucleus, axons, etc), with attributes including permeability, receptor density.
- 7. Functionality:** Software descriptions of cell functionality. Example: McCulloch-Pitts neuron model [10].

4. Example: Neural processes

Neural processes can be modeled by hierarchical invocation of LCM layers relating functionality with cellular mechanisms and structures. Software representations of axons, dendrons, and soma, from the physical layer, can be used to construct neuron networks. Objects from the metabolism layer model neuron energy states. The signal transduction layer can be invoked to simulate inter-neural synaptic/electrical communications mediated by intra-neuron signaling. Software for the

Hodgkin-Huxley equations, located in the biochemistry layer, can be executed as needed by upper layers.

5. Conclusion

The aims of morphoproteomics and whole-cell modeling, can be facilitated using the Layered Cell Model. Standards have to be defined that, for every layer, specify knowledge representations, mathematical algorithms, and temporal dynamics. Protocols for inter-layer communications and data sharing also need to be developed.

References

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