**Perspective: We need a modular framework for modeling signaling networks**

Outline:

1. Signaling networks are very complex and the current molecular-level focus hinders building models of multiple, interconnected signaling networks.
   1. Too fine a level: akin to building an operating system using assembly language
   2. Difficult to see principles from details (forests from trees)
2. Models are not reusable, forcing everyone to build their own models from scratch
3. Because regulation is distributed over a network, which contain multiple nested feedback loops, it is difficult to map functional changes to specific mechanisms. Thus, it is nearly impossible to design an effective compensation strategy
   1. Example of drug resistance as arising from “compensatory rewiring” of a signaling network
4. What is needed is a coarse-grain, modeling framework comprised of reusable “modules” that contain sufficient mechanistic details to permit mapping of molecular changes to phenotypic outcomes.
   1. This would be analogous to a higher-level programming language that subsumes the assembly language used to create its basic expressions.
5. This has been attempted at an abstract level, but not at a functional level
   1. Ad-hoc approach: no formal definitions
   2. Not demonstrated across different cell types or pathways
6. We feel that the most useful way to build a modular framework is to reverse-engineer the approach that cells actually use.
7. This would both exploit the “design patterns’ that cells have evolved to build the sophisticated signaling networks that orchestrate such complex processes such as development, wound healing and the immune response.
   1. Each of these processes require cells to dynamically respond to a complex, changing environment to reach a prespecified end state.
   2. Cells use remarkably few signaling pathways to accomplish this.
   3. Cells accomplish this by combining different pathway components/modules
8. Evidence has accumulated that pathways are indeed highly modular, thus facilitating their rearrangement and functional modification
   1. Give a few experimental examples: obvious ones are shedding and Grb2-Sos
   2. Give a few theoretical ones: Motifs would not work otherwise – arguments for evolutionary efficiencies
9. These identified modules appear to work across different receptor and cell systems
10. We propose that all signaling pathways are modular in nature and identifying the rules and molecular mechanisms that give rise to this modularity should be a central goal of systems biology
11. This approach could provide totally new insights into the “logic” of signaling networks.
    1. Example of affinity encoding for ligand systems
    2. Example of shortened relaxation time for induced endocytosis
12. For this to be achievable, need formal definitions of elements such as module interface, insulation, types of modules, etc
    1. Definition of unique versus shared components. Shared proteins are similar to global variable, unique to local variables.
    2. Definition of different types of modules
    3. Definition of “information”
    4. Assignment of control to specific molecules
    5. There is clearly a hierarchy of modules, like in OOP. How do you deal with this?
13. If this is done in a comprehensive way, then you could infer function from cell compositional data.
14. Conclude: We should be working together to understand the modular framework of cells and use this knowledge to create a formal modeling framework. This would lead to predictive rather than descriptive models and provide important insights into the design patterns used by evolution to build, and modify cell signaling networks.