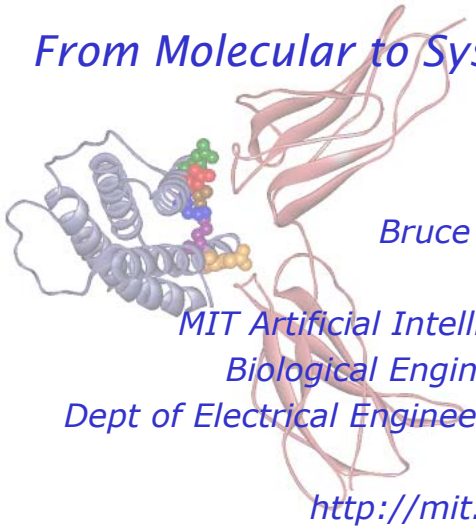
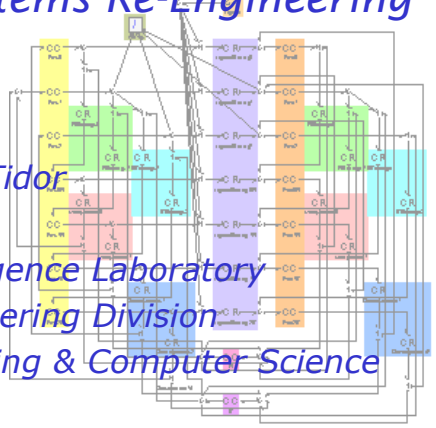
From Molecular to Systems Re-Engineering

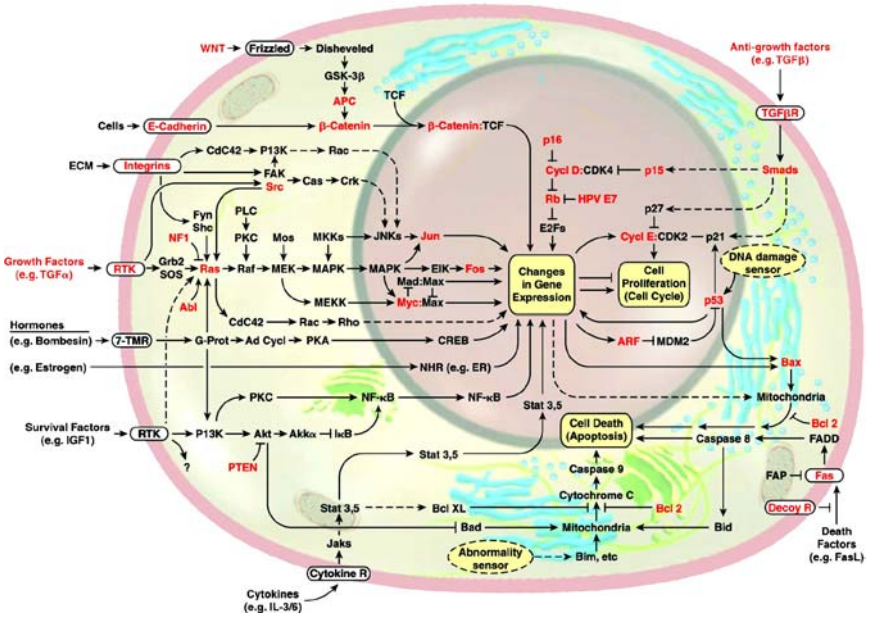




Bruce Tidor

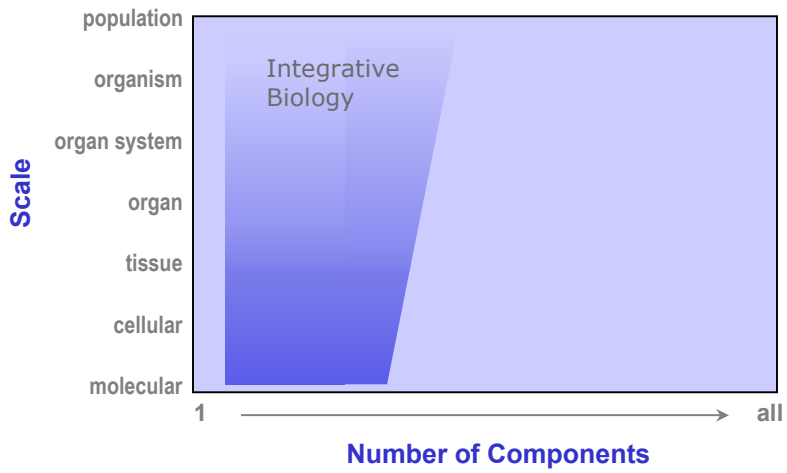
MIT Artificial Intelligence Laboratory
Biological Engineering Division
Dept of Electrical Engineering & Computer Science

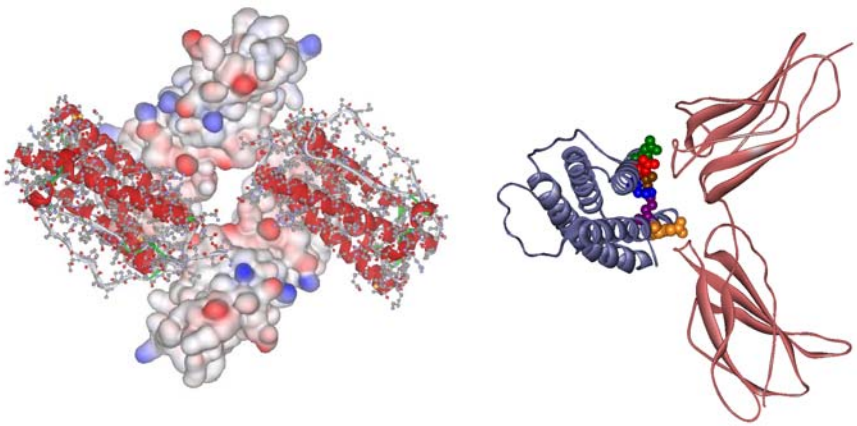
http://mit.edu/tidor



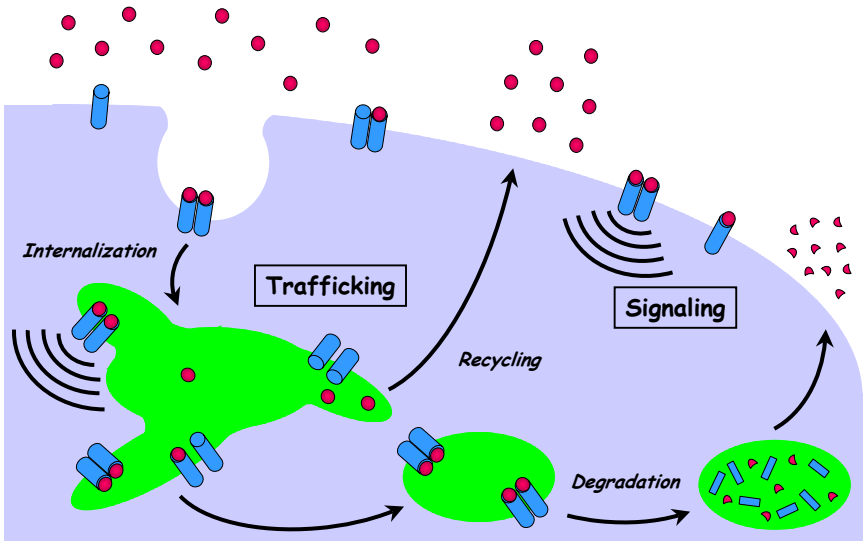
D Hanahan and RA Weinberg, *Cell* **100:** 57–70 (2000).

Horizontal and Vertical Systems Integration





Systems Level Approach to Drug Design



Cell-Level Pharmacokinetics

Extracellular Ligand

$$\frac{dL}{dt} = \left[- k_f L R_s + k_r C_s + k_{rec} L_i V_e N_A \right] \cdot \left(\frac{n}{N_A} \right)$$

Surface Receptors

$$\frac{d(nR_s)}{dt} = \left(- k_f L R_s + k_r C_s - k_{eR} R_s + V_s \right) \cdot n$$

Surface Complexes

$$\frac{d(nC_s)}{dt} = \left(k_f L R_s - k_r C_s - k_{int} C_s \right) \cdot n$$

Intracellular Ligand

$$\frac{d(nL_i)}{dt} = \left[- k_{fi} L_i R_i + k_{ri} C_i - k_{rec} L_i N_A V_e \right] \cdot \left(\frac{n}{N_A V_e} \right)$$

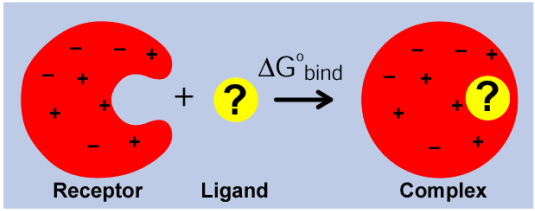
Intracellular Receptors

$$\frac{d(nR_i)}{dt} = \left(- k_{fi} L_i R_i + k_{ri} C_i + k_{eR} R_s - k_{deg} R_i \right) \cdot n$$

Intracellular Complexes

$$\frac{d(nC_i)}{dt} = \left(k_{fi} L_i R_i - k_{ri} C_i + k_{int} C_s - k_{deg} C_i \right) \cdot n$$

Theory for Electrostatic Complementarity



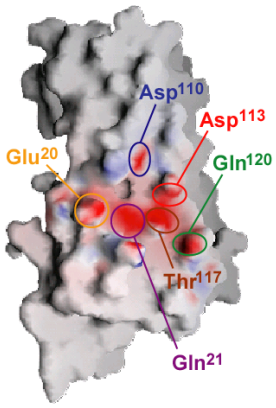
$$\Delta G^\circ_{bind} = \Delta G^\circ_{inter,\ LR} + \Delta G^\circ_{hyd,L} + \Delta G^\circ_{hyd,R} + \Delta G^\circ_{non\text{-}elect}$$

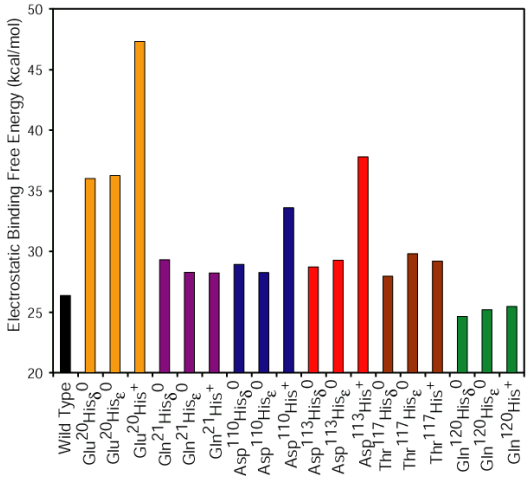
$$\Delta G^\circ_{var} = \Delta G^\circ_{inter,\ LR} + \Delta G^\circ_{hyd,L}$$

$$= \vec{Q}^T \vec{A} + \vec{Q}^T \leftrightarrow \vec{B} \vec{Q}$$

$$\boxed{\vec{Q}^{opt} = -\frac{1}{2} \leftrightarrow B^{-1} \vec{A}}$$

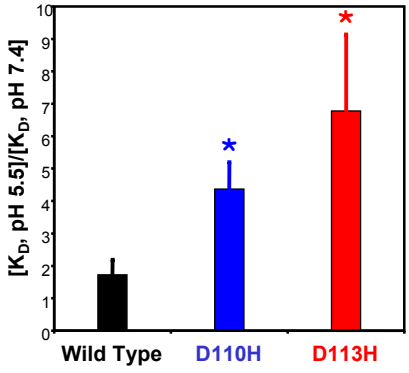
L-P Lee & B Tidor, *J Chem Phys* **106:** 8681–8690 (1997).
E Kangas & B Tidor, *J Chem Phys* **109:** 7522–7545 (1998).
E Kangas & B Tidor, *Phys Rev E* **59:** 5958–5961 (1999).



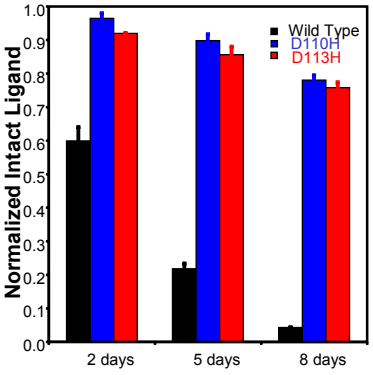


CA Sarkar et al., *Nature Biotechnol* **20:** 908–913 (2002).

Histidine Mutants Exhibit pH-Dependent Binding

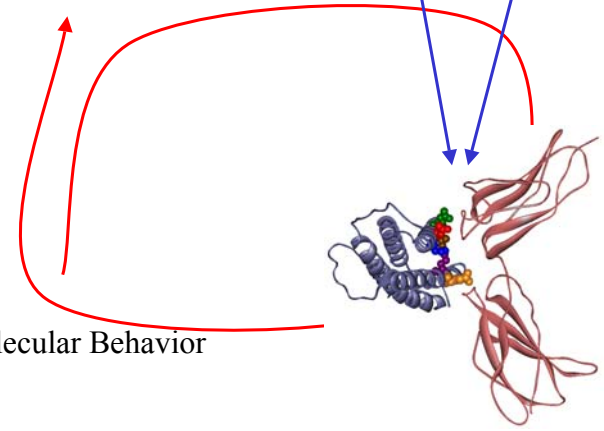


Mutants Have 10-Fold Longer Half-Lives Than Wild Type



Cellular Behavior

$$\frac{d(nC_i)}{dt} = \left(k_{fi}L_iR_i - k_{ri}C_i + k_{int}C_s - k_{deg}C_i\right)\cdot n$$



Molecular Behavior