



Welcome!

*Why do we need a Consortium?
What is down the road?*

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Systems Biology: What are the Roots?

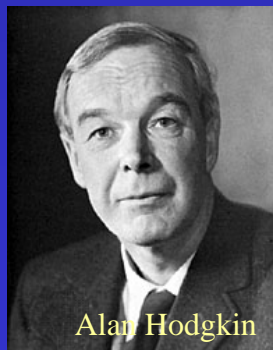
I. Quantitative biology and mathematical modeling



Fibonacci (Leonardo Pisano), 1170-1250.
1202 – in “*Liber abaci*” a recursive relation for a rabbit population, $F(n) = F(n-1) + F(n-2)$,
1, 1, 2, 3, 5, 8, 13, 21, 34, 55, ...

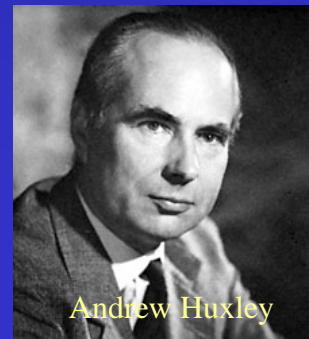


1913 - Maud Menten and Leonor Michaelis derived the Michaelis-Menten equation.
1944 - Maud Menten published one of the first use of electrophoresis to separate proteins



Alan Hodgkin

In 1952, Hodgkin and Huxley explained the mechanism of the generation of an action potential and described mathematically the dependence of Na^+ and K^+ channel conductance on the membrane potential and time



Andrew Huxley

Systems Biology: What are the Roots?

II. Systems and Control Theories in Engineering and Biology



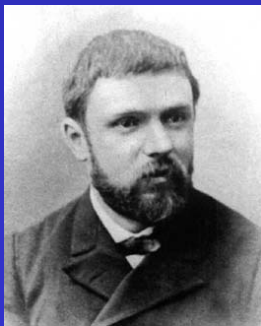
Ludwig von Bertalanffy. *General System Theory*, 1967.
“The concept of system has pervaded all fields of science and penetrated into popular thinking, jargon and media.”

Systems theories, such as MCA, BST, and FBA

III. Quantitative Data Mining

~Omics: Genomics, Proteomics, Metabolomics...

However, do not forget:

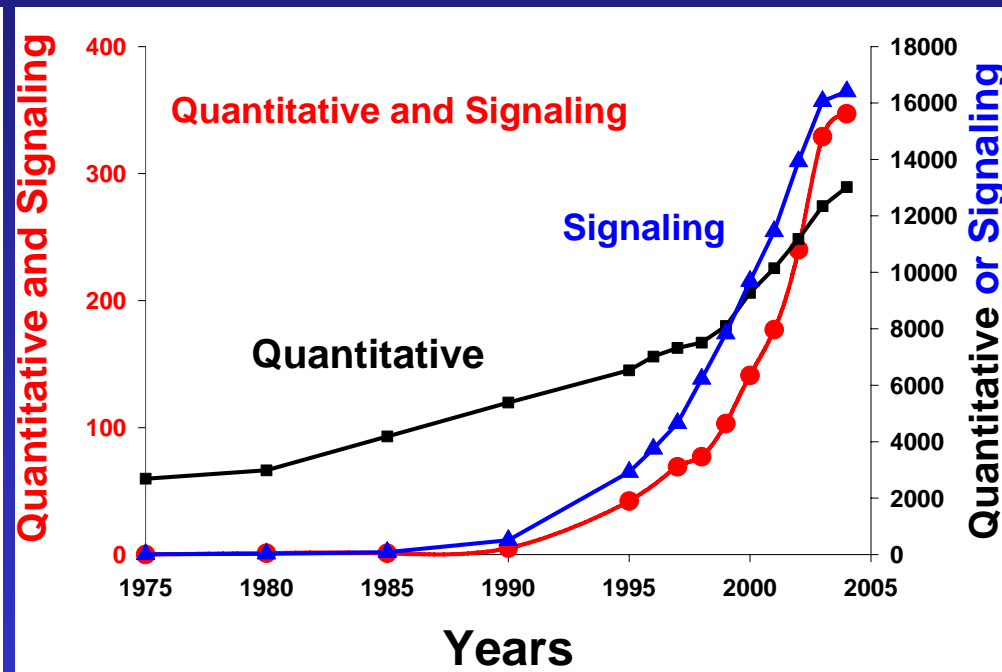
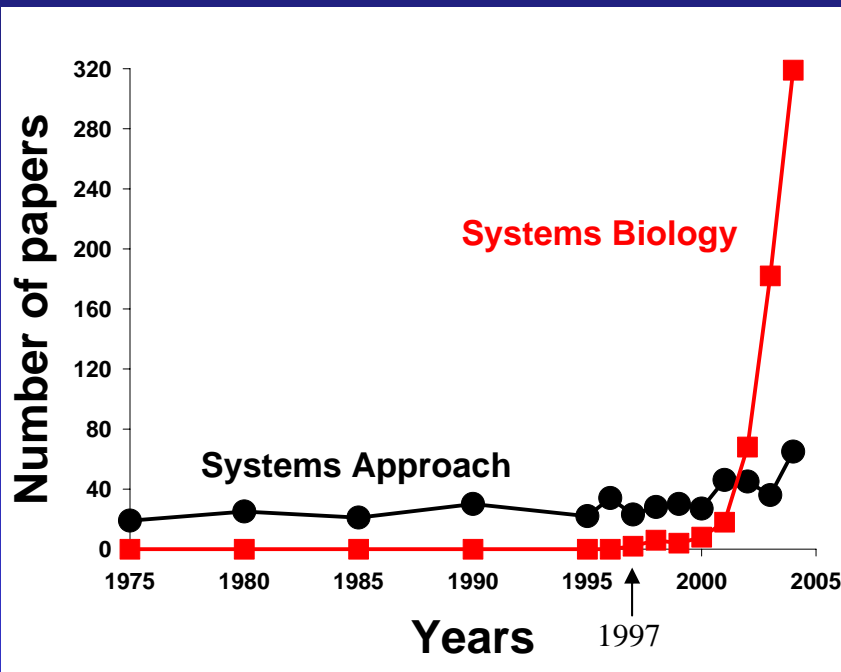


Henri Poincaré (1854-1912) was a mathematician, philosopher, and a bard of science. “Science is built up of facts, as a house is with stones. But a collection of facts is no more science than a heap of stones is a house”.

Biology has always studied systems

However, studies of signal transduction were mostly *qualitative*

A dramatic increase in the amount of quantitative data is a key difference from previous studies



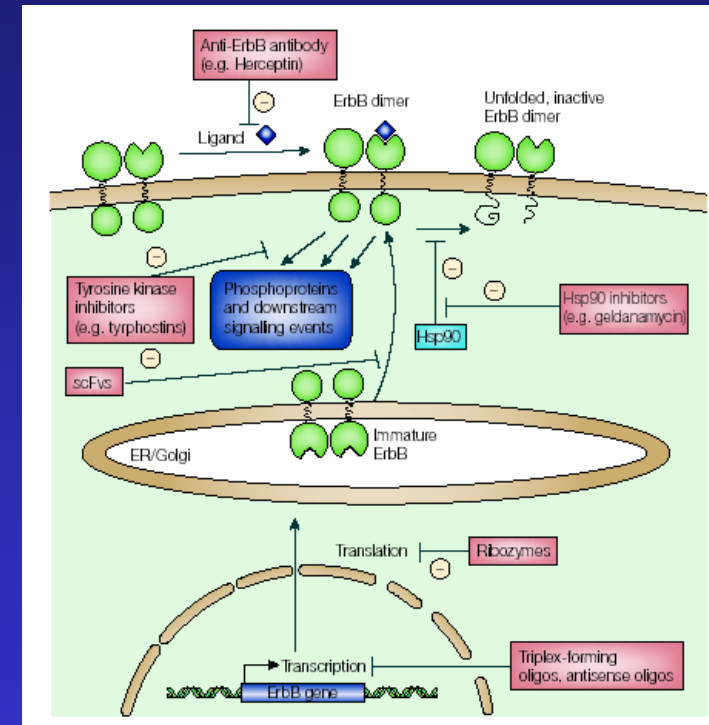
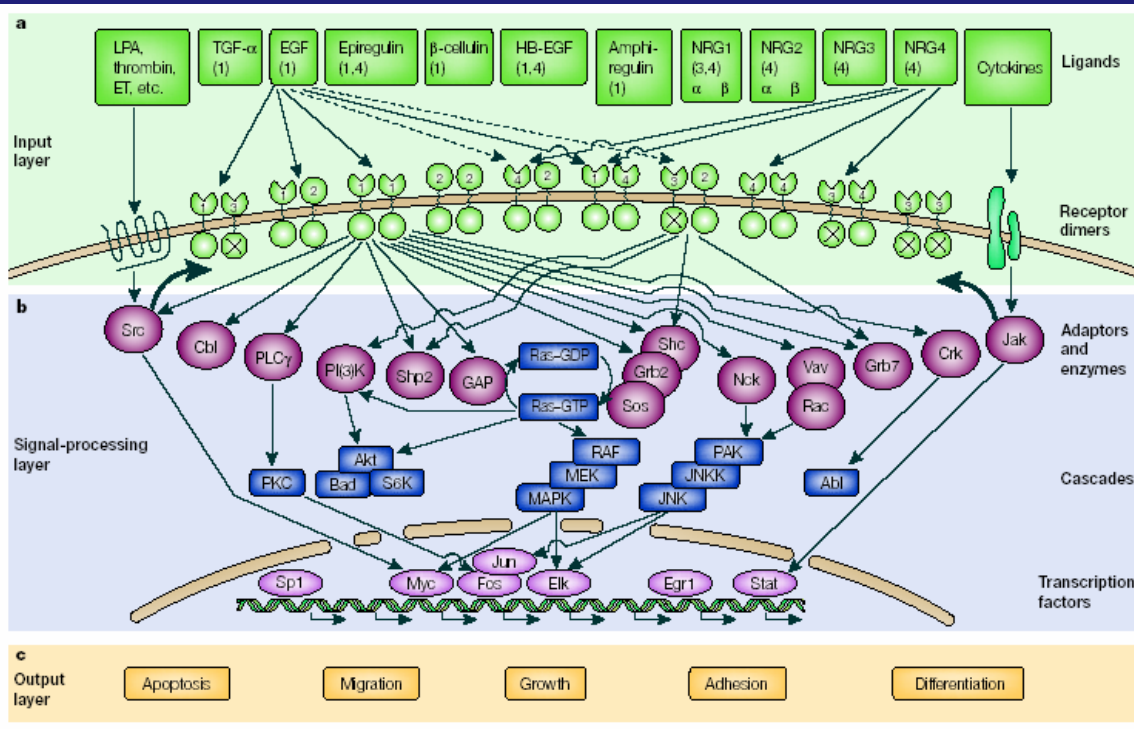
1997 - Systems Biology Research Unit, Glaxo

1999 - Institute of Systems Biology

Systems Biology has exploded
in the last 5 years!

Quantification of Signal Transduction has
not yet become a major research area!

The complexity of the ErbB receptor signaling networks: Multiplicity of players and interactions



Yarden & Sliwkowski (2001) Nature Reviews: Mol Cell Biol. 2:127.

International Consortium: Systems Biology of RTK Networks

- **We need Systems Biology**

- to deal with complexity rationally and efficiently

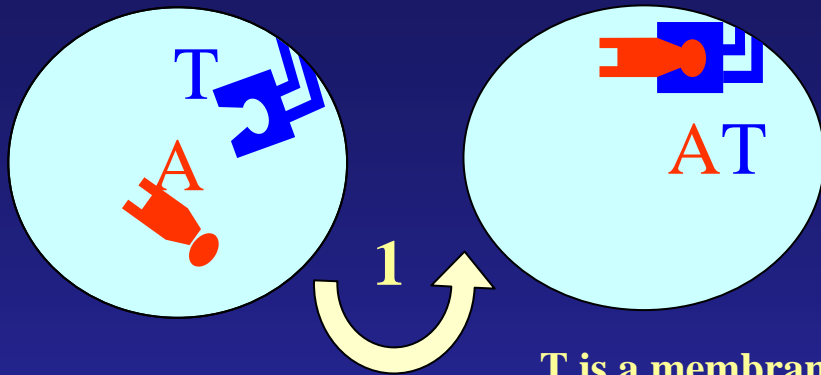
- **We need a Consortium that brings together the best labs worldwide**

- to facilitate research on quantitative understanding of cell signaling

- to harness the synergistic effort of geneticists, molecular and cell biologists, chemists, engineers, mathematicians, and physicists

- to strengthen collaboration between academia and industry

How Receptor/Lipid-Mediated Membrane Recruitment Drives the Chemical Transformation



Membrane anchoring of only one of two interacting proteins does not change the reaction rate significantly

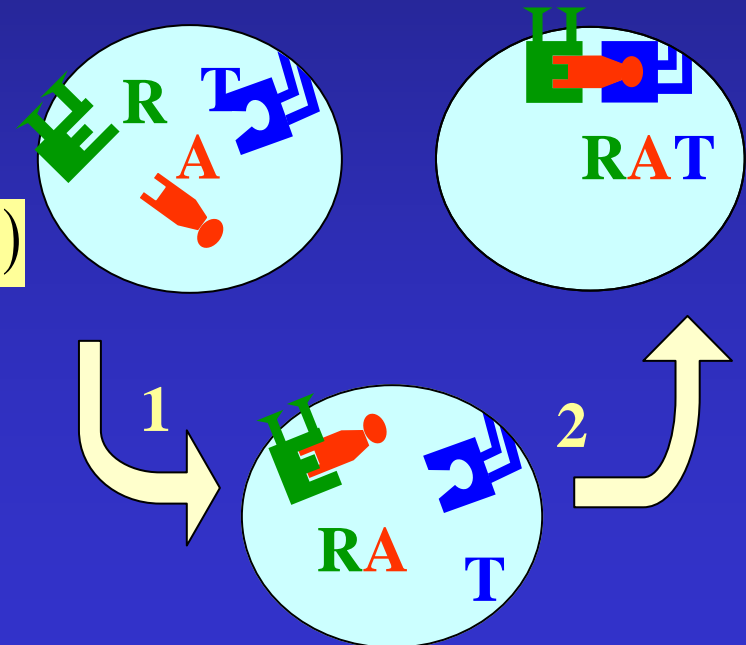
T is a membrane-anchored target protein. A is a cytosolic protein.
R is a membrane receptor

Receptor-mediated membrane recruitment enhances the number of signaling complexes and reaction rates

$$K_{assoc}^{app} (\text{piggyback riding}) = K_{assoc} \cdot (V_c / V_m) / (1 + \kappa)$$

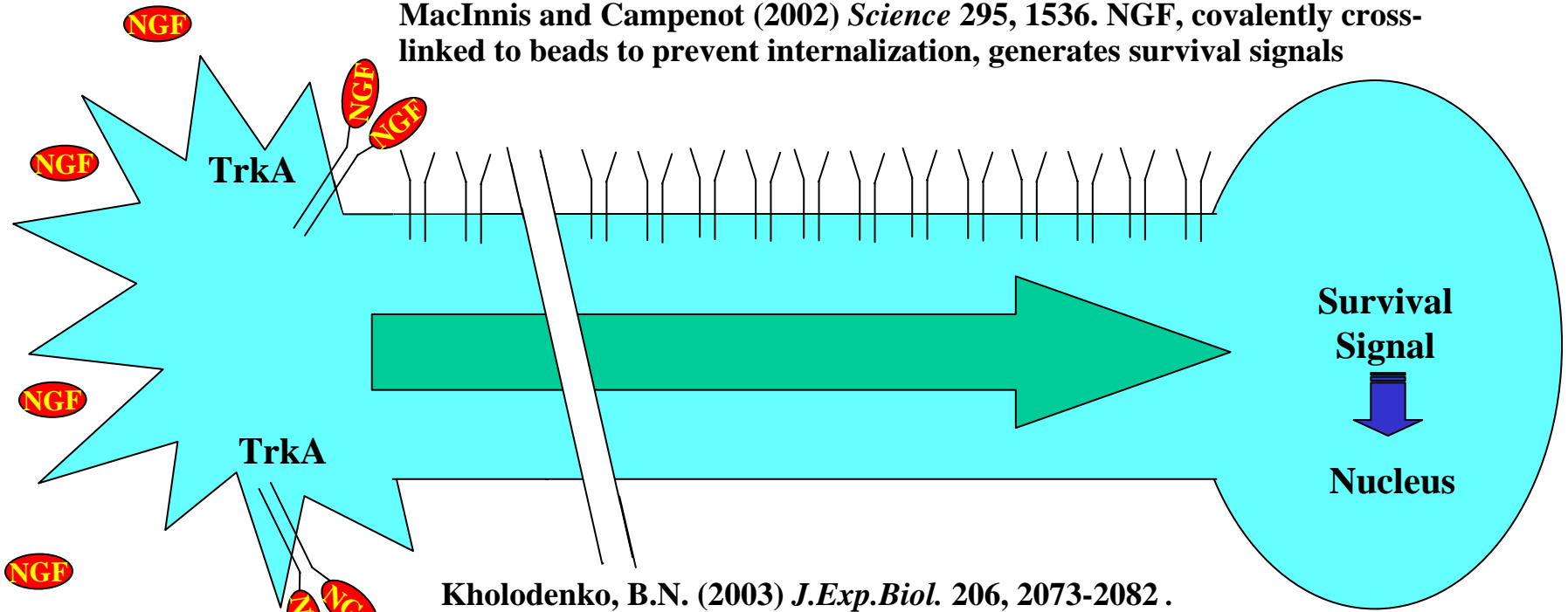
$\kappa = (K_d^R / C_R)$ appear to be less than 1

The apparent association constant for proteins A and T increases by a factor of 300 or more (V_c is the cytosol volume, V_m is the volume of the shell where these proteins are confined).



Cellular Pathways for Long-Range Signaling

MacInnis and Campenot (2002) *Science* 295, 1536. NGF, covalently cross-linked to beads to prevent internalization, generates survival signals

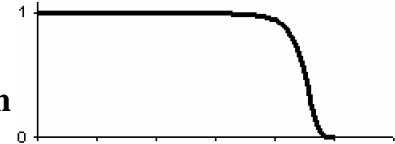


Kholodenko, B.N. (2003) *J.Exp.Biol.* 206, 2073-2082.

A traveling wave solution to the Fisher-like equation

$$\frac{\partial a}{\partial t} = D \cdot \frac{\partial^2 a}{\partial x^2} + ka(c - a) - v_p(a)$$

Ligand-independent wave of TrkA activation



Challenges: Depending on whom you ask ...

•Development of experimental technologies

- quantitative high-throughput assays at single cell, population, and tissue levels;
- model systems approaching in vivo situation (3D-culture, zebrafish...)
- abundance of RTK network proteins, e.g. kinases, in different cells/tissues

•Integration of data from genetics and biochemistry to cell/tissue biology in the form of “Knowledge” databases amenable for systems analysis and modeling

- More than data compendium

•Development of modeling concepts and computational technologies

- Multiple scales in time and space
- Molecular dynamics
- Kinetic modeling
- Stochastic modeling,...

Further Challenges

- **Quantitative understanding of Network Organization**

- Identification of common signaling motifs for diverse functions – taking lessons from model systems and evolution (e.g., MAPK cascades)

- **Integrative modeling of RTK pathways and gene expression response**

- **Increased understanding of receptor/pathway specificity, e.g. IR versus IGF-1R, and cell-fate decisions**

- **Identify targets crucial for the mitogenic potential of cancer cells versus normal cells employing computational modeling of RTK pathways**

Points of Discussion

- **What do we need for a successful RTK consortium?**
- **How do we make the RTK consortium work?**
- **Organization/Work/Funding**
 - How should the RTK consortium be organized?
 - Science is always competitive. How can we encourage members to collaborate?
 - Developing standards to compare and integrate experimental and modeling results between labs and industry groups worldwide?
 - Setting standards for quality in methods and modeling?
 - How can joint projects be funded?
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