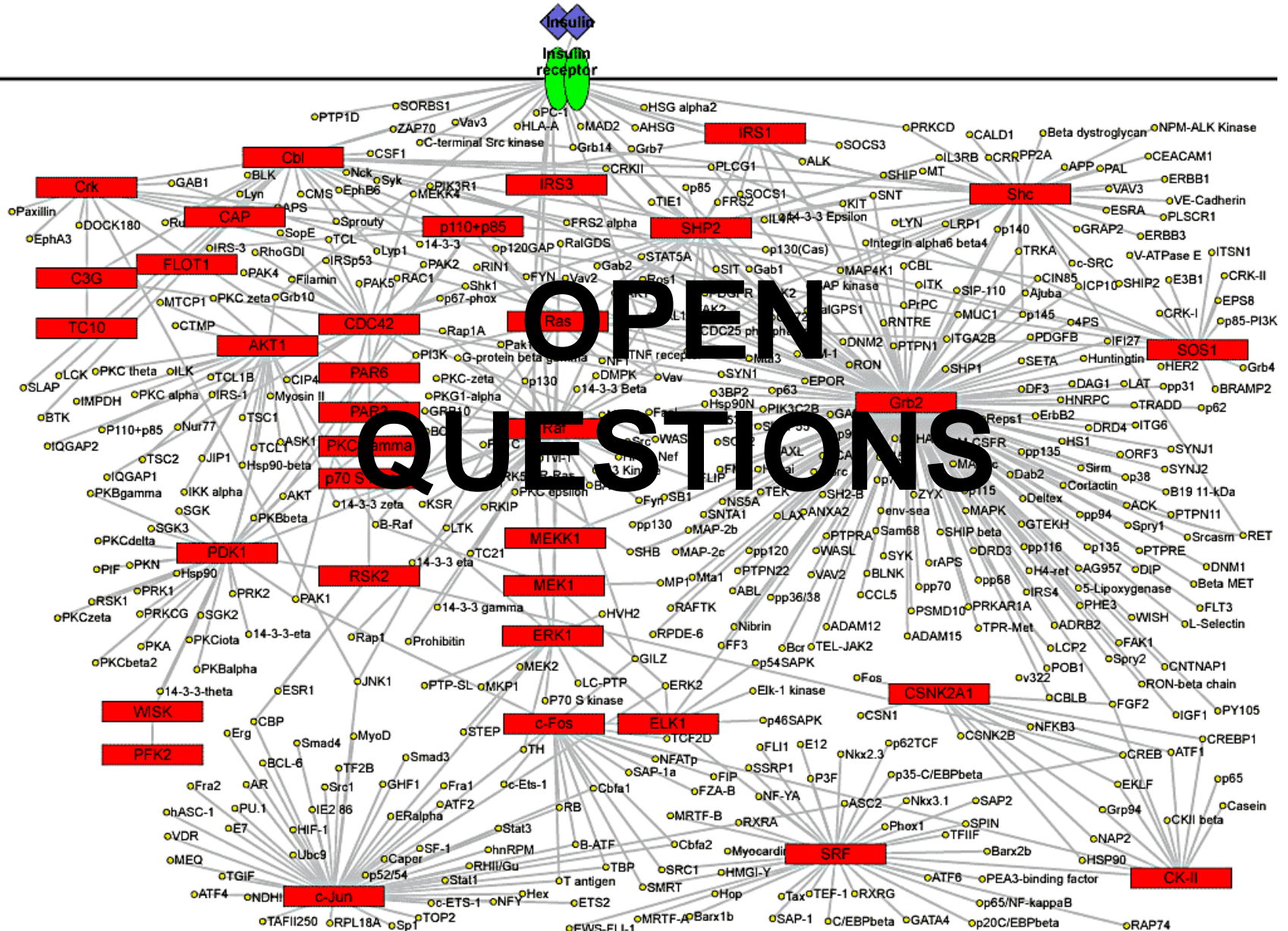
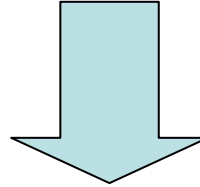


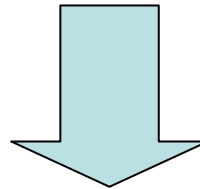
Towards a Systems Biology of RTK Signal Transduction



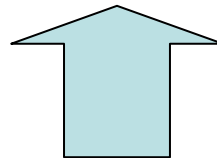
VISION



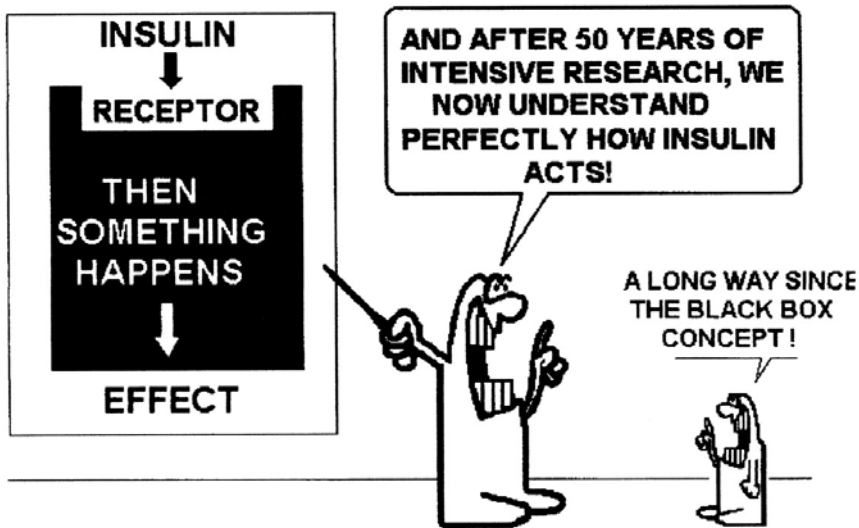
STRATEGY



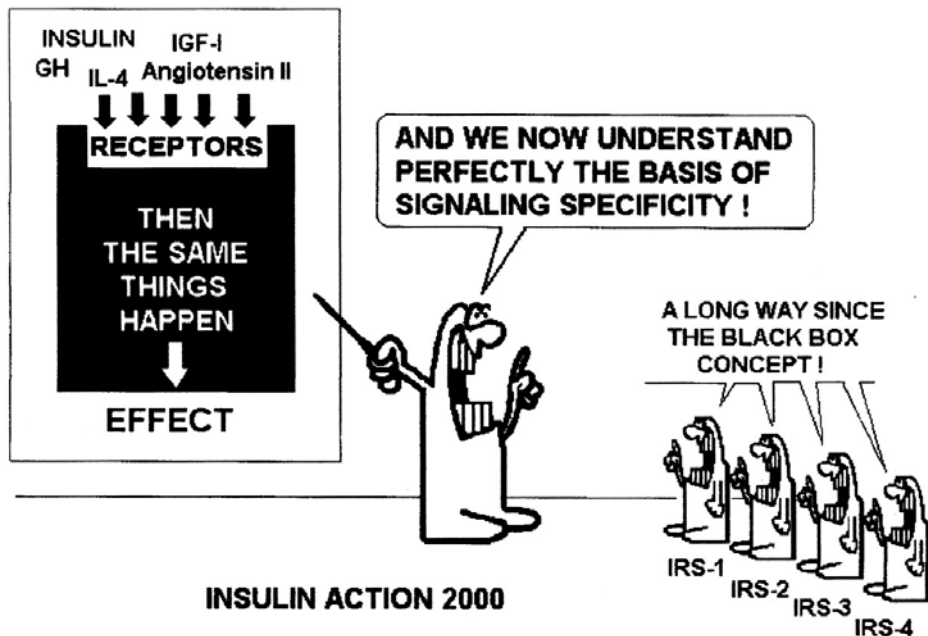
TACTICS



Identify hurdles



INSULIN ACTION 1977

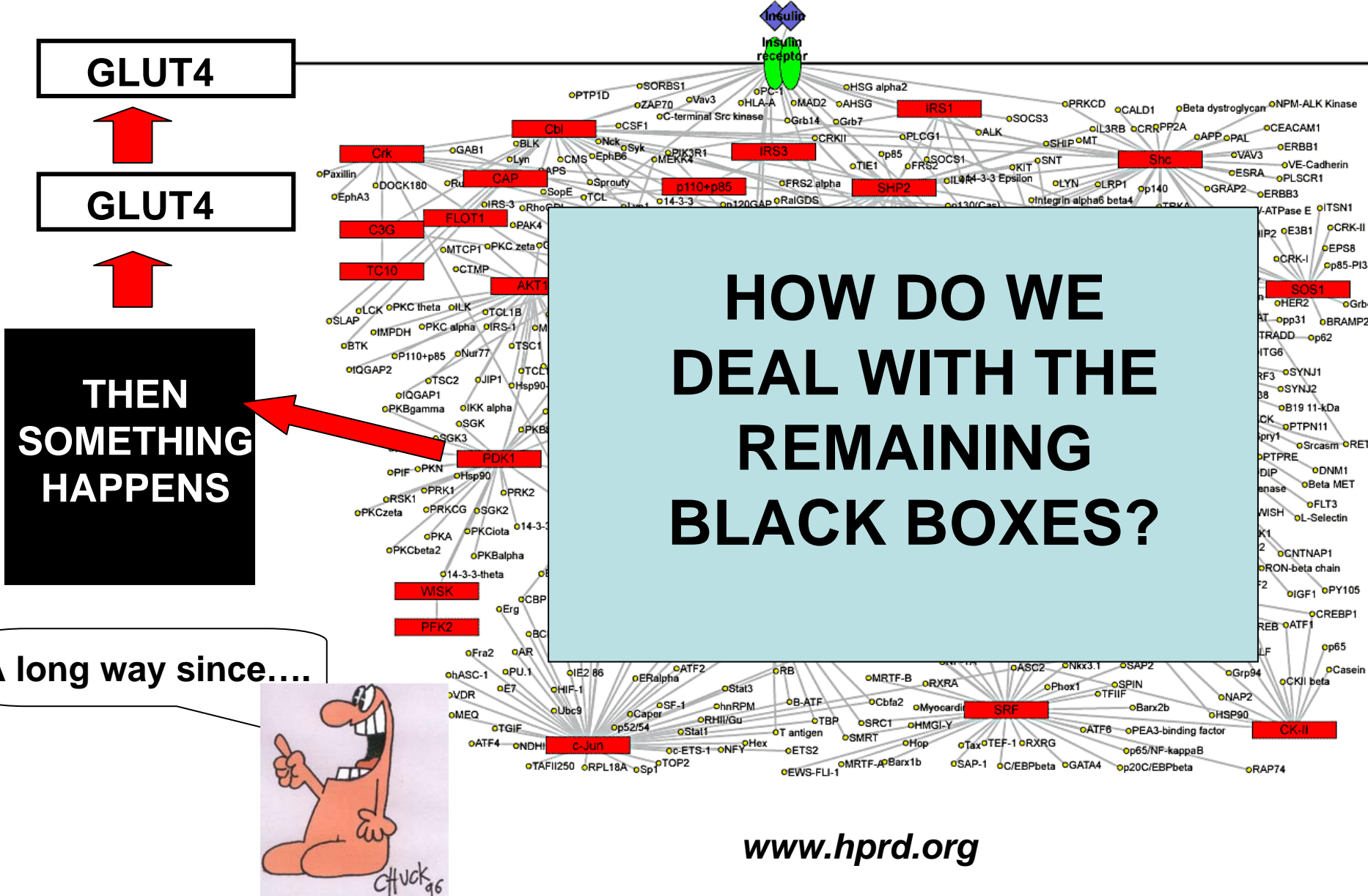


INSULIN ACTION 2000

The signaling paradox

Redrawn for Dumont JE et al.,
Am J Physiol 283:C2-28, 2002

Insulin action 2004



Modeling of regulatory networks: how to choose the best methods?

- **Directed and undirected graphs**
- **Bayesian networks**
- **Boolean networks**
- **Generalized logical networks**
- **Piecewise linear differential equations**
- **Qualitative differential equations**
- **Partial differential equations**
- **Rule-based simulation formalisms**
- **Groupoid theory**
- **???**

Insulin
Insulin
receptor

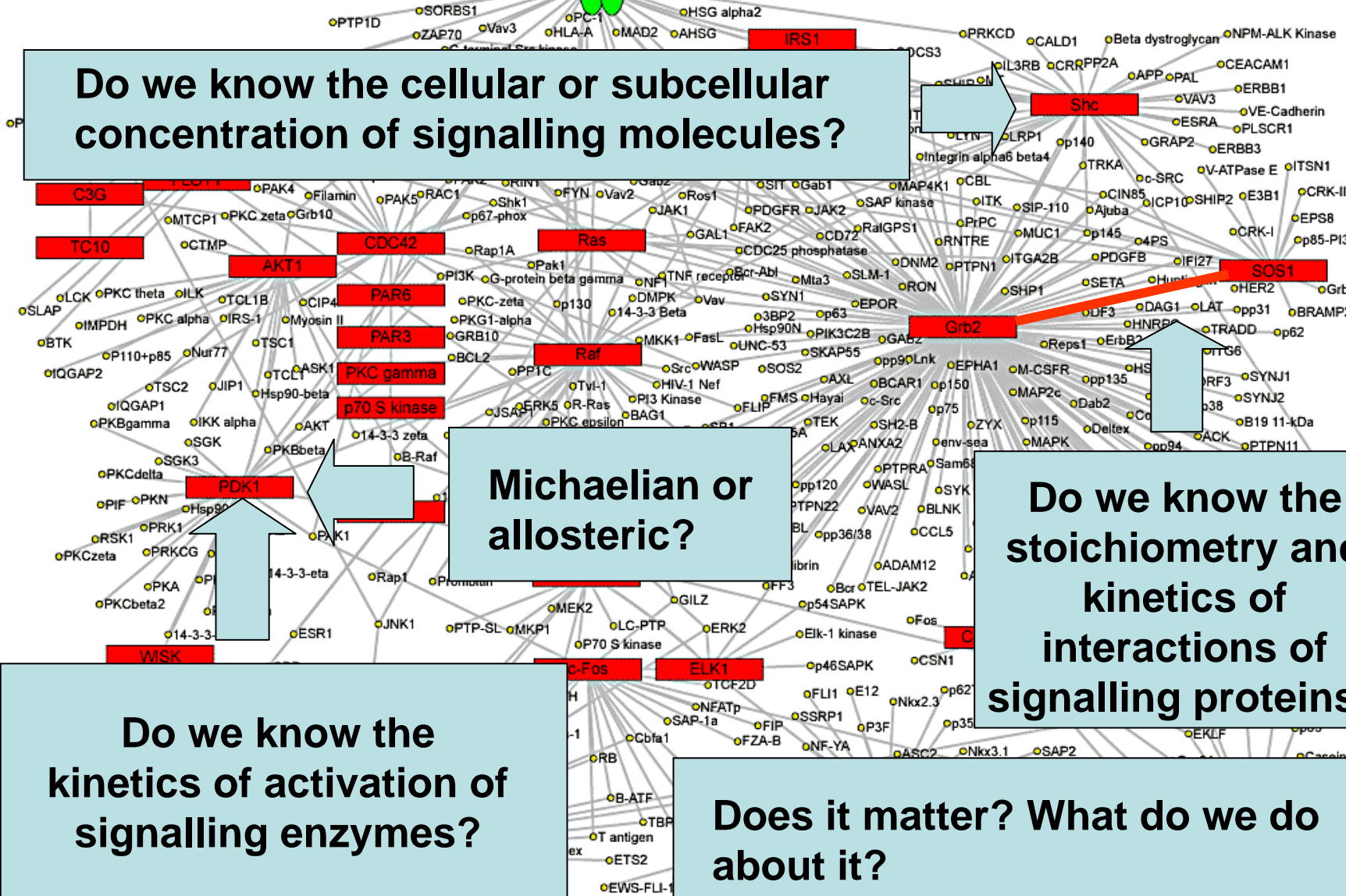
Do we know the cellular or subcellular concentration of signalling molecules?

Michaelian or allosteric?

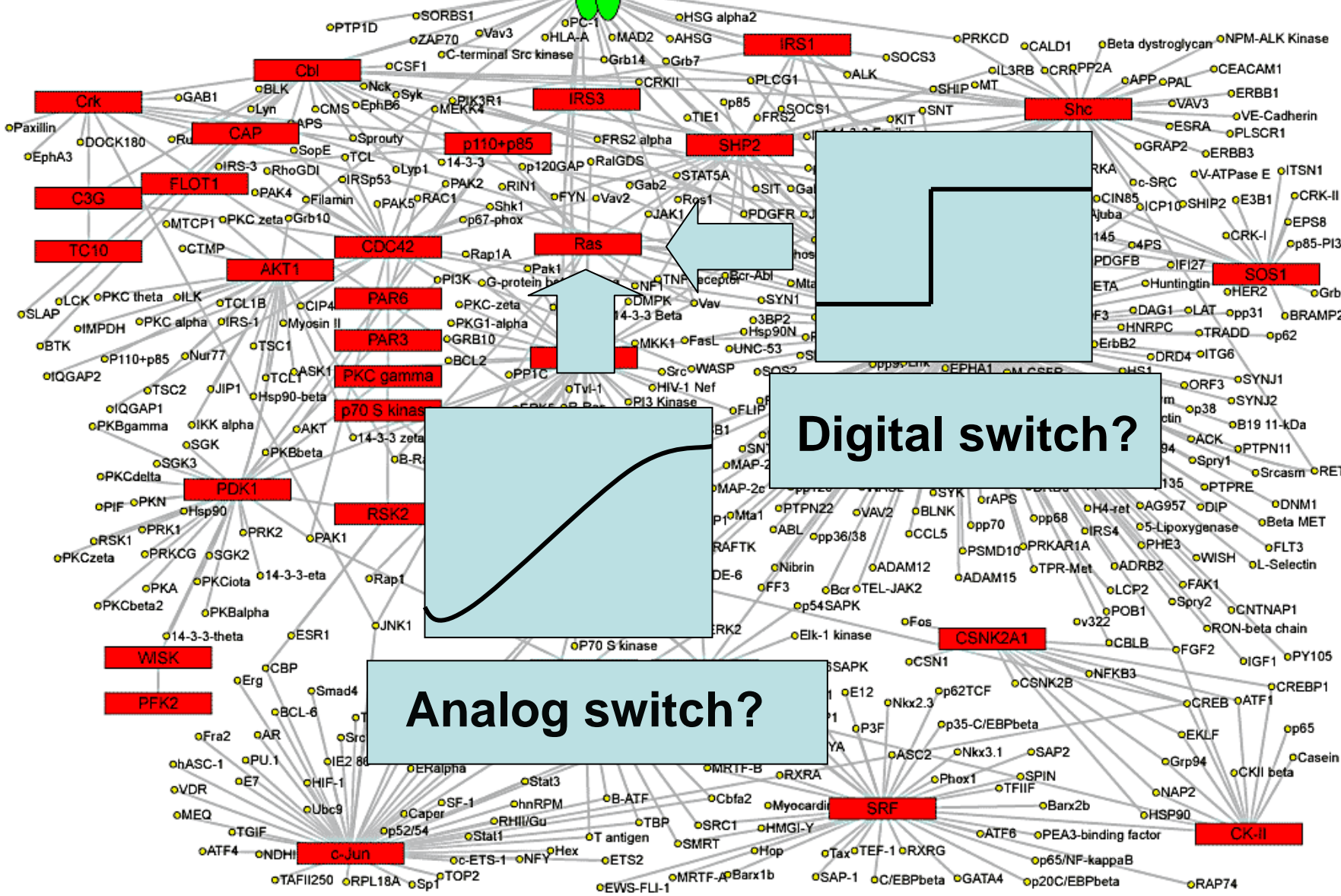
Do we know the stoichiometry and kinetics of interactions of signalling proteins?

Do we know the kinetics of activation of signalling enzymes?

Does it matter? What do we do about it?



Insulin
receptor



Digital switch?

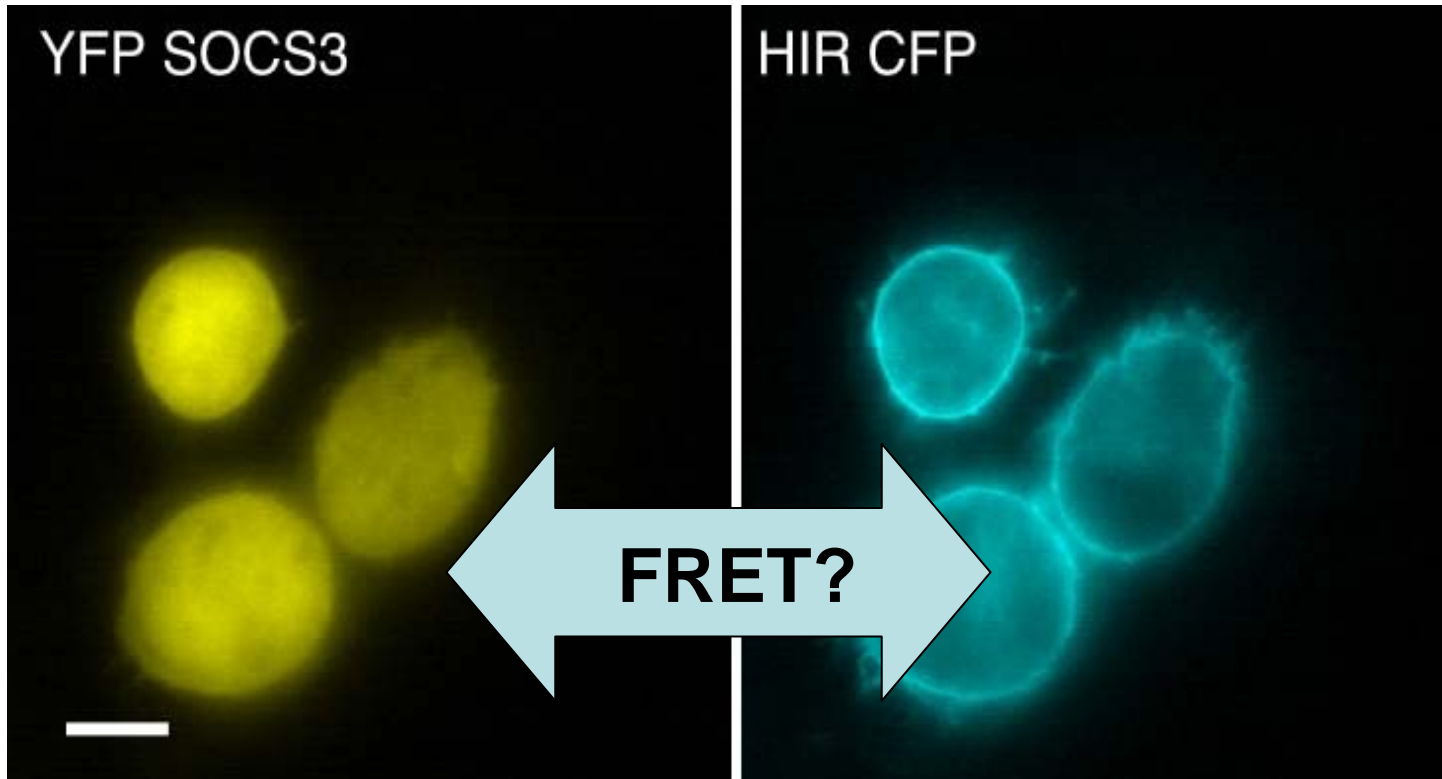
Analog switch?

CK-II

**How do we integrate
cooperative ligand binding
or cooperative node
activation into models of
signalling networks?**

Different ligand-induced receptor dimerization/oligomerization models (monovalent or bivalent ligand, one or more subsites per receptor...) have different equilibrium and kinetic characteristics. Does this have consequences for the dynamics of downstream signaling?

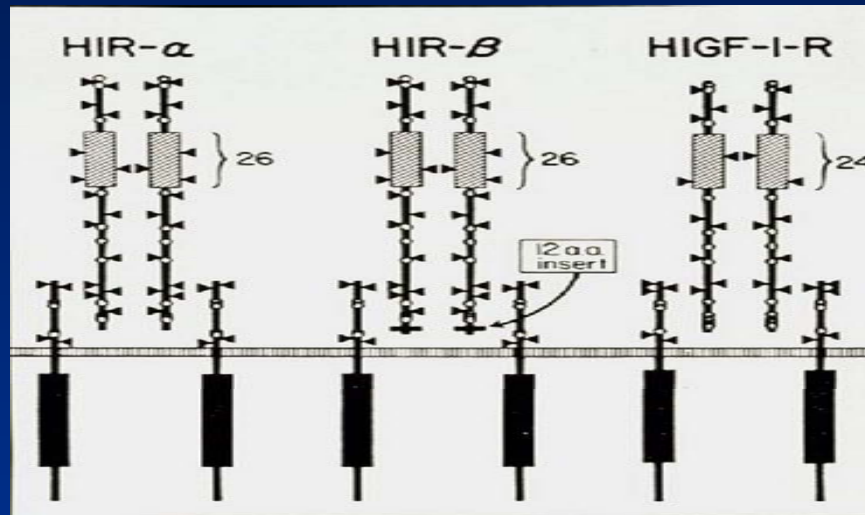
Bell-shaped curves!



Can we transform quantitative cellular imaging of protein localization/interactions (FRET, BRET) into quantitative subcellular kinetics?

Insulin **Insulin analogues** **IGF-II** **IGF-I**

REAL-TIME KINETICS



siRNAs

THE REVERSE ENGINEERING PROBLEM

cDNA Microarray Gene Analysis



The beginning?