From molecular events to clinical outcome: Computational systems biology in the pharmaceutical industry

Klaus Prank

Scientific Computing & Mathematical Modeling (SCMM)
PCIT, R&D IT, GlaxoSmithKline
Stevenage, UK

ICSB 2006, Yokohama
9 October 2006

Agenda

- History of drug discovery and systems biology
- Linking physiology- and target-based drug discovery
- Pharmaceutical interest in pathways and modeling
- Modeling EGF/ErbB – signaling
- Challenges in large-scale pathway modeling
- Modeling the heart: Cardiac liability
- Conclusions

History of drug discovery and systems biology

- **Historically:** Herbal drugs discovered through observations in patients
- ~ 1900 **Modern Drug Discovery:**
  - Derivatives of natural products and novel synthetic chemicals
  - Screening still in the setting of complex disease biology
  - Animals replacing patients as primary ‘guinea pigs’
- Replacing animal models through:
  - Tissue-level screens (e.g. vascular or tracheal muscle tone)
  - Cell-based pathway screens (e.g. proliferation, cytokine production)
  - Ultra-high-throughput screens of individual molecular targets with hundreds of thousands of compounds a day
- Powerful for known, validated targets
- Disappointingly few new drugs found when applied to less well biologically understood targets (e.g. genome-derived)

History of drug discovery and systems biology

- Knowing a target does not mean knowing what the target does.
- Effects of an inhibitor on the target in diverse disease settings might be unknown.
- Enormous investment in genomics and screening technologies in the past 20 years.
- However: Costs for drug discovery rise, while approval rates fall.
- Primary selection of drug targets and candidates divorced from the complexity of disease physiology.
- **We are re-entering systems biology, in modern guise!**

What is systems biology?

Academic definition

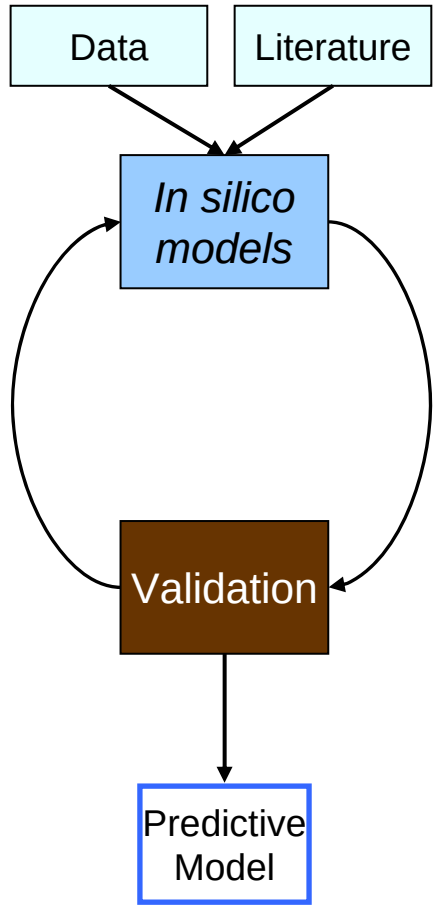
1. Systems biology seeks to integrate different levels of information to understand how biological systems function. (http://en.wikipedia.org/wiki/Systems_biology)

2. Systems biology is the global analyses (and/or modeling) of many data types together. Each data type gives you different and unique aspects of a system.

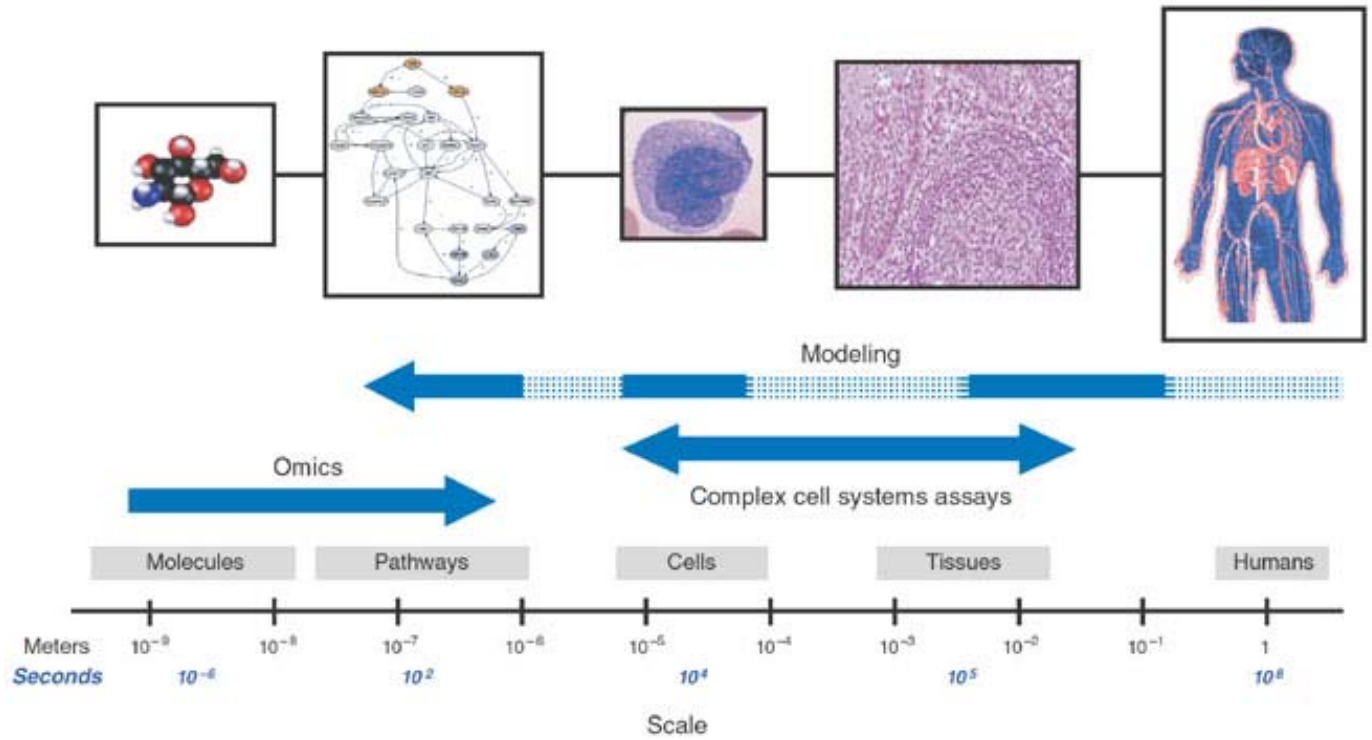
Industry definition

1. Improve the value chain of drug discovery and development by using systems biology.

2. The aim of systems biology in medicines discovery and development is to optimize decisions in discovery, development and application of new chemical entities based on hypothesis driven research.



Linking physiology- and target-based drug discovery through modeling

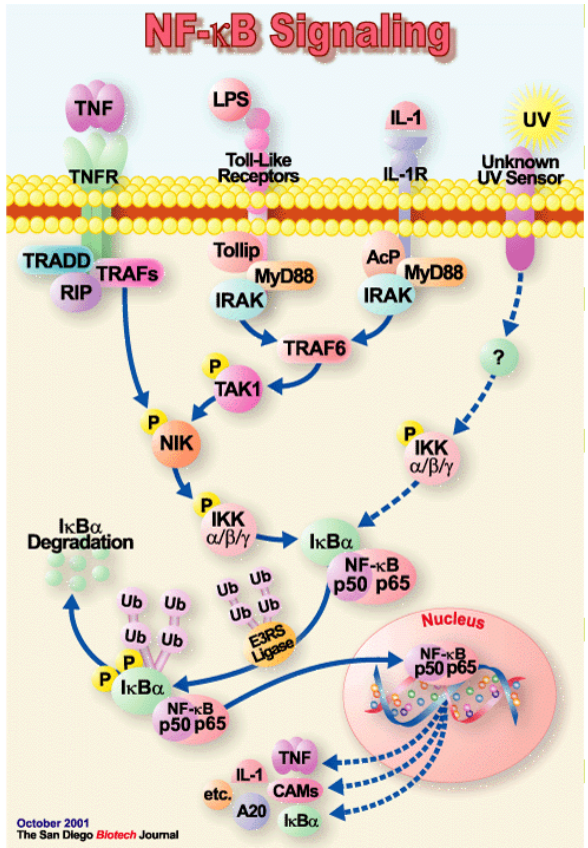


Linking biological levels is part of what system biology is about. Best example is the heart.

Molecular signaling pathways: A new grammar for drug discovery

Moving beyond individual genes and proteins:
Signaling pathways intuitively hard to understand systems!!

- Multiple receptors, multiple compartments
- Feedback loops, e.g. gene-protein
- Pathways intersect, i.e. cross-talk
- Complex, nonlinear system dynamics
  i.e. temporal and/or amplitude regulation of target genes
- Pathway kinetics vary between cells
- Pathway outputs have different effects in different contexts, i.e. complex disease outcomes
- Pathway are mechanistic foundation for disease description.

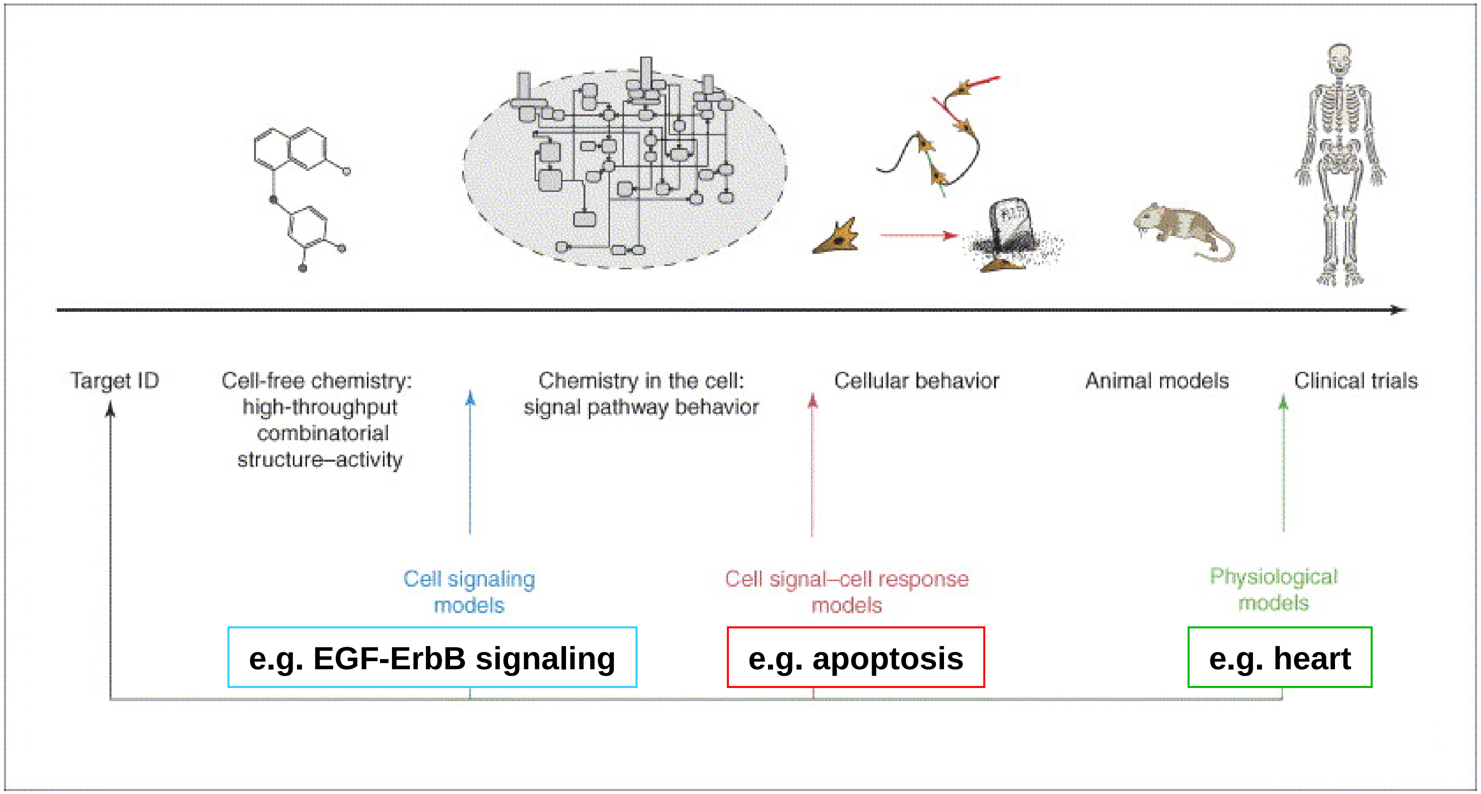


Qualitative, static thinking fails:
Become quantitative and dynamic → model and compute!

Interest in signaling pathways in the pharmaceutical industry

- Predicting culture conditions for overproduction of biopharmaceuticals
- Understanding compound modes of action
- Mechanistic understanding of cardiac and liver liability
- Identifying novel behaviors and new behaviors of known pathways
  - Clues to new intervention approaches
  - Selecting and prioritizing of new targets
- Identifying and validating bio-markers
  - Animal ↔ human correlation
- Interpreting and integrating systems biology data:
  - Transcriptomics, proteomics and metabolomics and other ‘omics’

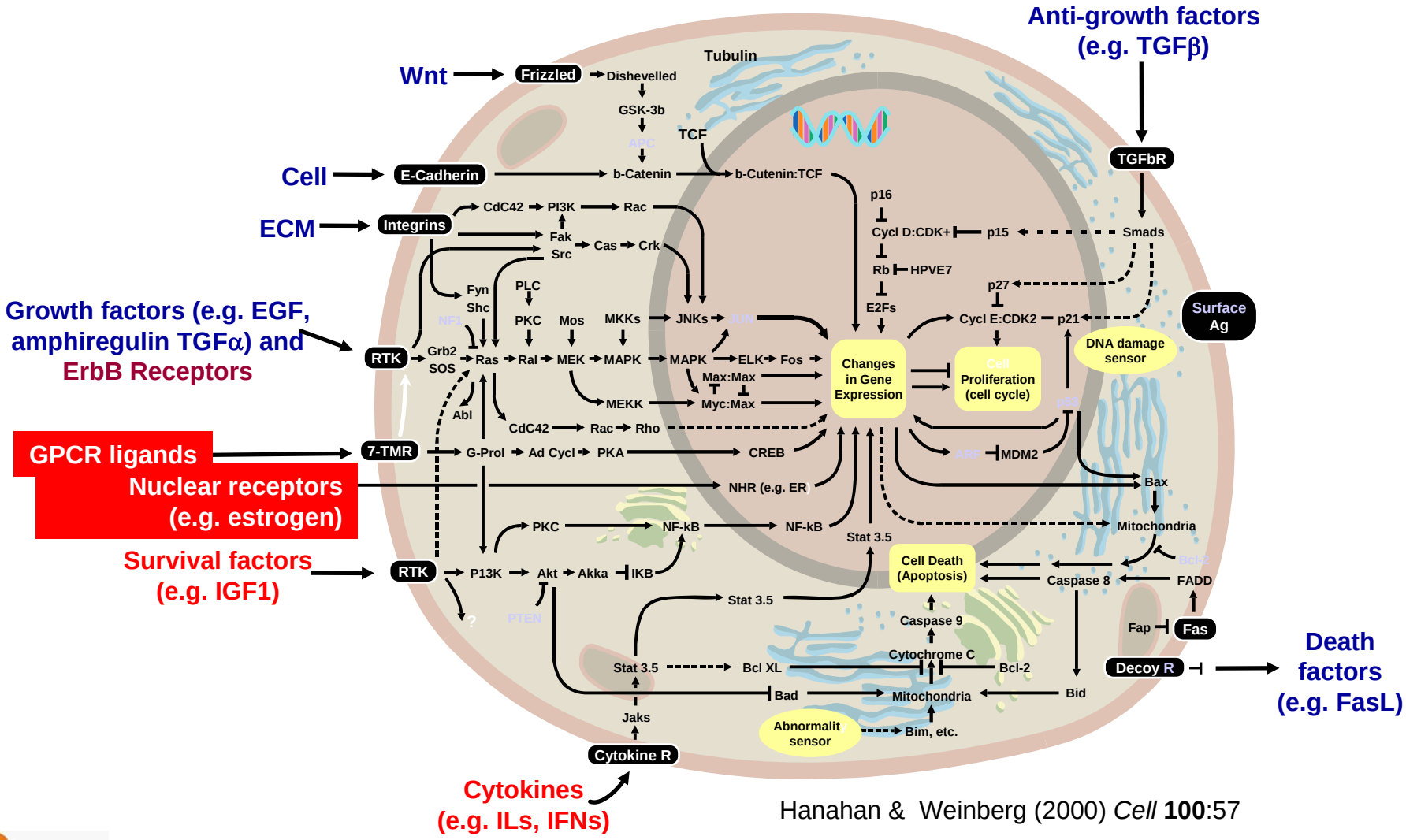
Areas of computational modeling in the pharmaceutical R&D process.



Wednesday, October 11th, 10:30-12:30
SYSTEMS BIOLOGY FOR MEDICINE: Signal Transduction
Boris N. Kholodenko: "Cell-signaling dynamics in time and space"
Mariko Hatakeyama: "Ligand-dependent cell fate control of ErbB signaling network in breast cancer cells"

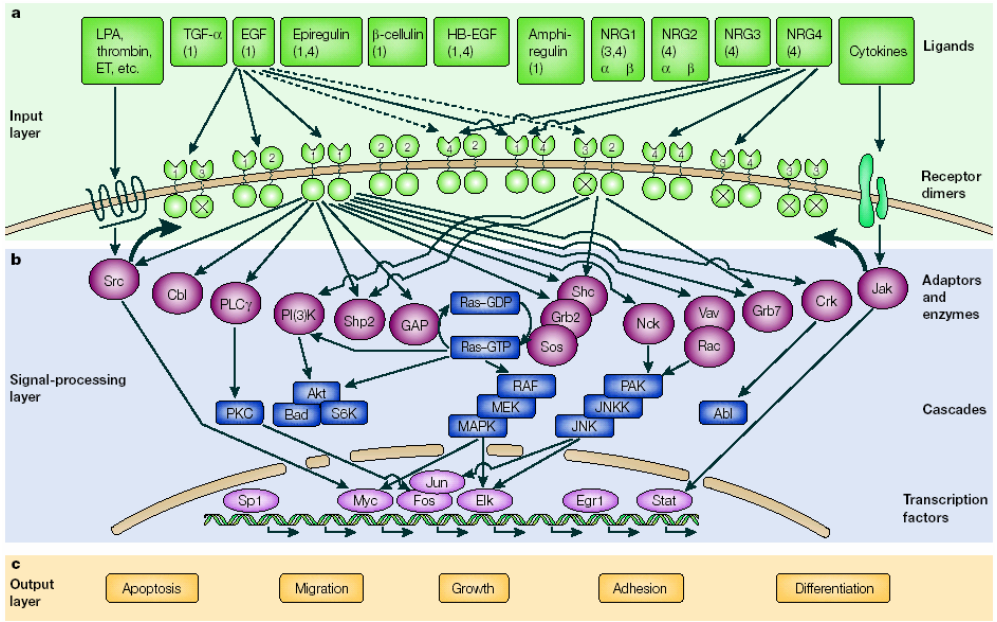
Tuesday, October 10th, 14:00-16:00
SYSTEMS OF BASIC BIOMEDICAL SYSTEMS: Cardiovascular Systems Biology
Giovanni Paternostro: "Cardiac systems biology"
Akira Noma: "Kyoto model, a comprehensive cardiac cell model"

EGF-ErbB-receptor network well studied signal transduction system



Hanahan & Weinberg (2000) *Cell* **100**:57

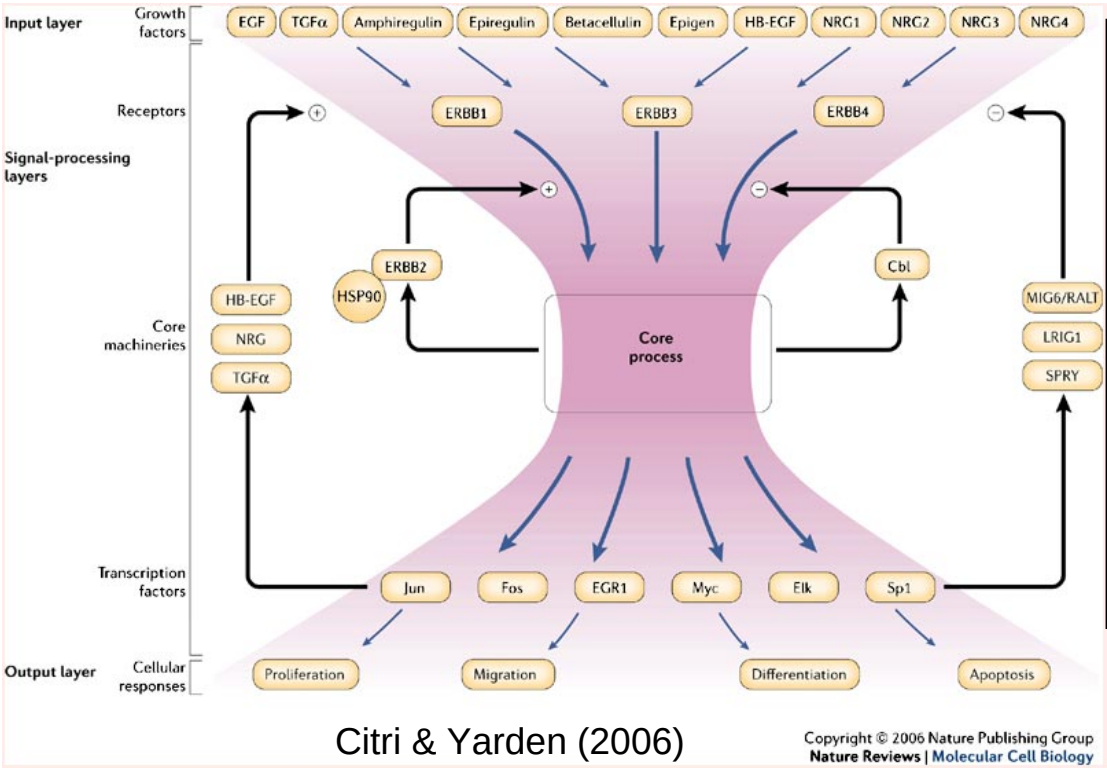
Cell signaling models: EGF-ErbB signaling



Yarden & Sliwkowski (2001)

- ErbB receptors and signaling pathways are implicated in various cancers
- ErbB pathway hyper-activated in various cancer cell lines by different mechanisms
  (mutations, overproduction or constitutive activation of receptors).
- Target of several cancer drugs
- Systems-level understanding through modeling is expected to generate therapeutic opportunities to intercept aberrant network activation

A systems perspective of the ErbB network



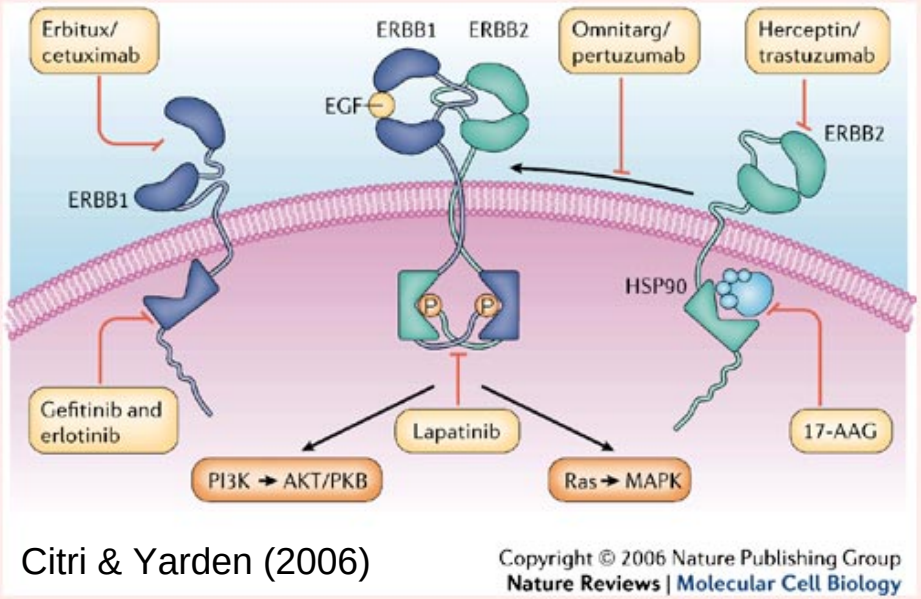
Citri & Yarden (2006)

Dynamical control of amplitude, kinetics and frequency of output signals by:

- Positive-feedback loops
- Negative-feedback loops
- Buffering
- Subcellular compartmentalization
  - Endocytosis of ErbB1
  - Endocytosis/signaling interface
  - Translocation of ErbB proteins to the nucleus

Bow-tie-architecture:
Input of multiple growth factors that function through 8 potential receptor hetero- or homodimers activate common signaling cascades (core process) that results that lead to selected cell fate.

Network fragility: ErbB's as pharmaceutical targets



Citri & Yarden (2006)

- **Anti-ErbB antibodies:**
  - Herceptin (Genentech, ErbB2)
  - Erbitux (Bristol Myers Squibb, ErbB1)
  - Omnitarg (Heterodimerization of ErbB2)
- **Tyrosine-kinase inhibitors:**
  - Gefitinib (Iressa, AstraZeneca, ErbB1)
  - Erlotinib (Tarceva, Genentech, ErbB1)
  - Lapatinib (Tykerb, GSK, ErbB1, ErbB2)
- **Inhibitors of heat-shock-protein-90 (HSP90)**
  - ErbB2 strictly dependent on HSP90 chaperone complex for maintenance of its stability
- **Drug combination**
  - Targeting multiple components of ErbB network
  - Integration of anti-ErbB drugs with chemo- and radiotherapy improves outcome and can overcome drugs resistance

Models of ErbB network

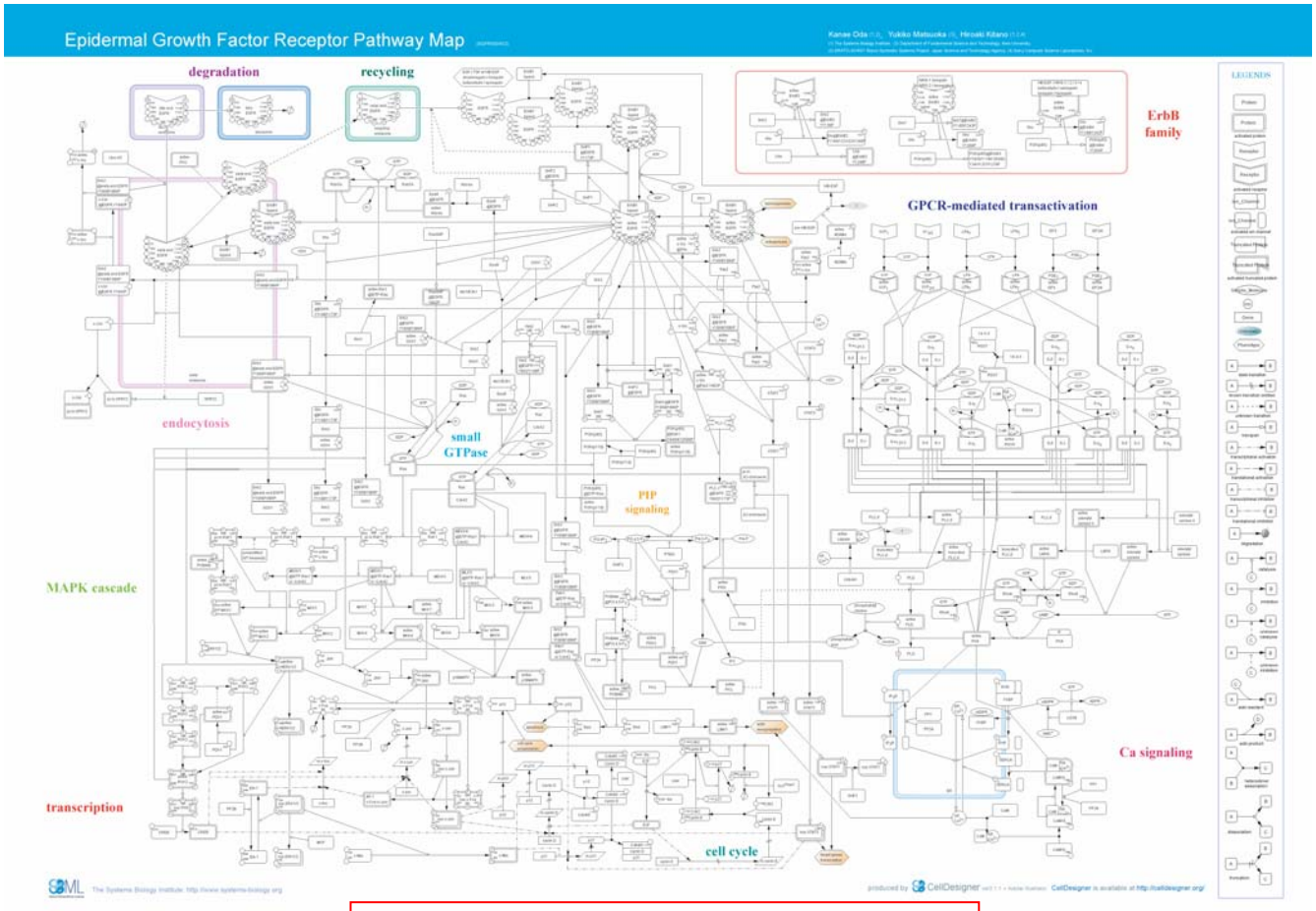
- Original models addressed questions of EGF-receptor binding and internalization
  - Wiley & Cunningham (1981) *Cell* **25**:433.
- Expansion of models to relationship of receptor-ligand interactions to cell proliferation
  - Starbuck & Lauffenburger (1992) *Biotechnol. Prog.* **8**:132.
- Expansion to early steps of receptor trafficking
  - Wiley et al. (1991) *J. Biol. Chem.* **266**:11083

  .
- Rapidly evolving models that address signaling events:
  - Kholodenko *et al.* (1999) *J. Biol. Chem.* **274**:30169.
  - Schoeberl *et al.* (2002) *Nature Biotechnol.* **20**:370.
  - Resat *et al.* (2003) *Biophys. J.* **85**:730.
  - Maly *et al.* (2004) *Biophys. J.* **86**:10.
  - ...

Future of modeling ErbB network

- Modeling ErbB network just a prelude to be embedded in a larger network:
  - GPCR, cell-adhesion machineries, nuclear responses and other networks interfacing with ErbB signaling
- ErbB signaling is so pivotal to some of the most virulent human malignancies
- Reliable quantitative modeling is the basis for identifying new targets for cancer therapy
- Predict the consequences of combining specific drugs and clinical procedures
- Explain mechanisms of autoresistance to ErbB tyrosine kinase inhibitors and predict new therapeutic strategies

Modeling ErbB signaling network



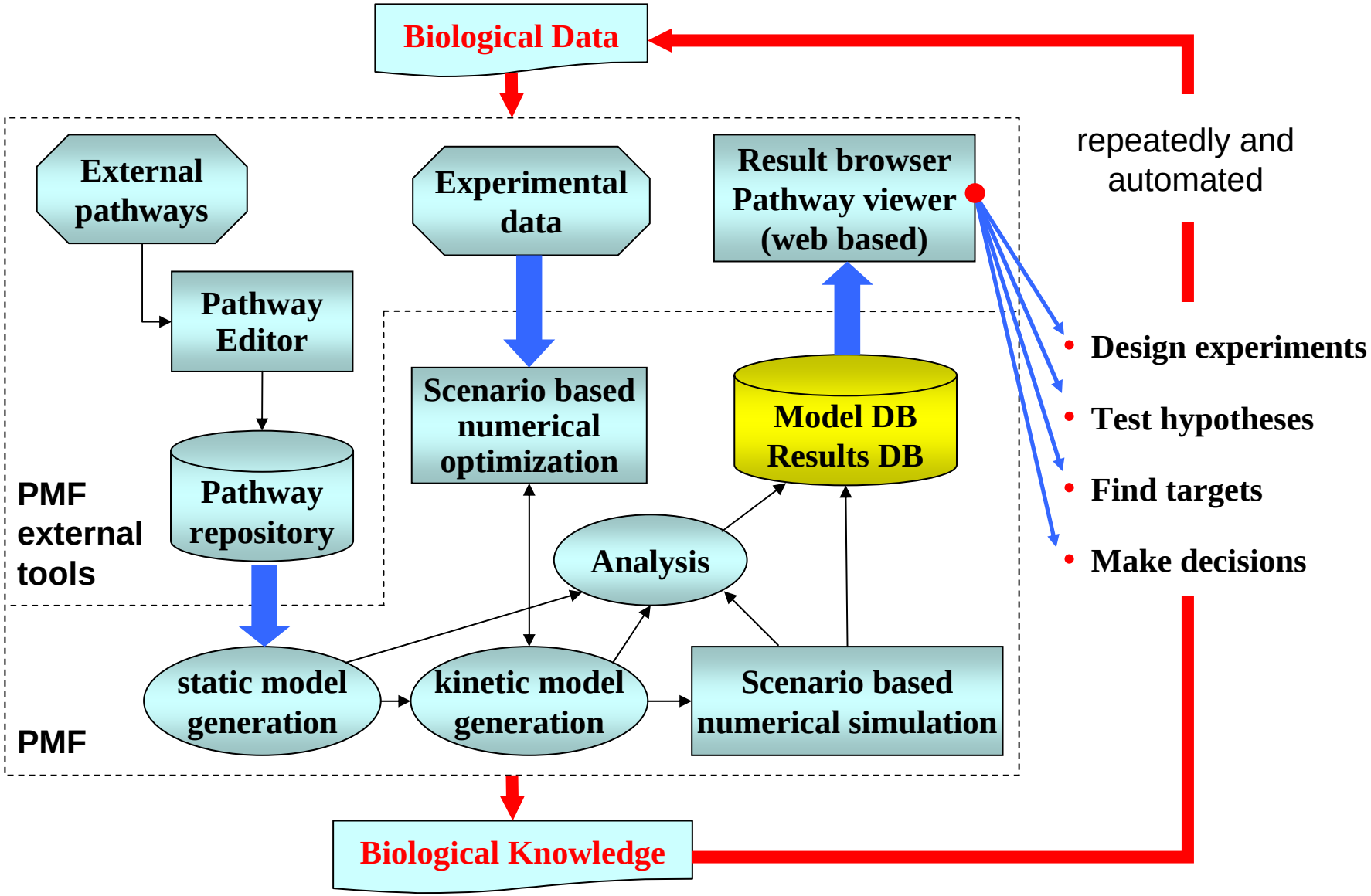
Oda *et al.* (2005) *Mol. Sys. Biol.* **1**:8.

Comprehensive pathway map of ErbB signaling network (211 reactions and 322 species) might function as a platform for generating models of higher complexity.

Challenges in large-scale pathway modeling

- Building the model
  - Knowledge management, incomplete knowledge
  - Updating knowledge and model – versioning
  - Automation
- Parameter challenges
  - More parameters compared to the experiments
  - Parameter guessing
- Model analysis
  - Too much for a human to peruse
  - Theory gaps for large systems
  - Automation
- Analysis and visualization/animation of simulation results
  - Too much for a human to peruse
  - New techniques
  - Automation

Pathway Modeling Factory (PMF) Concept



Modeling the heart: Cardiac liability

- More than 50% of drug withdrawals since 1997 attributed to cardiac side-effects
- Impacting **all** therapeutics drug classes
- Delay of ventricular repolarization and QT interval prolongation are major regulatory concerns
  → **increased risk of life-threatening ventricular tachyarrhythmia, particularly Torsades de Pointes (TdP)**

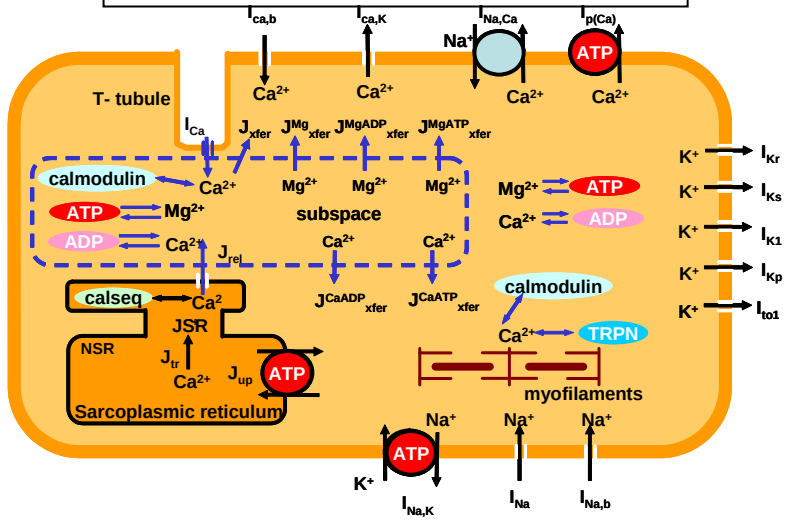
Modeling the heart: Cardiac liability

- Assessing pro-arrhythmic potential of drug candidates should be done early in preclinical development
- Avoid economic and public health consequences:
  - Late stage failures of drug candidates
  - Restricted labeling
  - Withdrawals of FDA-approved drugs
- Variety of *in vitro* and *in vivo* models for assessing QT prolongation and pro-arrhythmic potential of a drug candidate
- However, no single preclinical model proven to be predictive surrogate for the human heart

Mechanistic understanding of cardiac liability

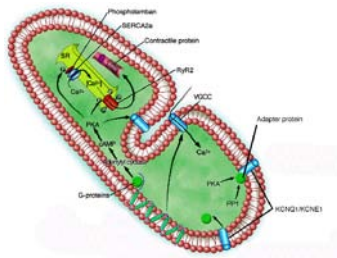
- Cardiac repolarization terminates cardiac action potential (AP)
- Results from activities of multiple membrane ion channels and transporters
- Interaction through membrane potential and intra/-extracellular ionic concentrations
- Also effected by systemic factors
  - Hormone regulation, metabolic state,
  - Autonomic nervous tone
- Variety of mechanisms could contribute to abnormal repolarization of the heart

Drugs can change behavior of one or more ion channels

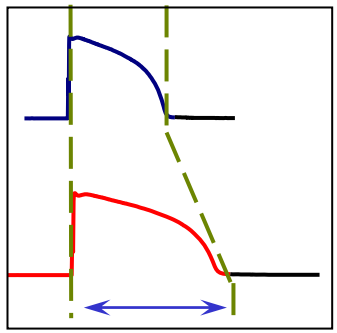


Mathematical myocyte model

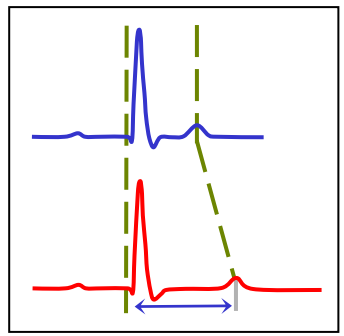
[Michailova & McCulloch (2001) *Biophys J.*]



Myocyte



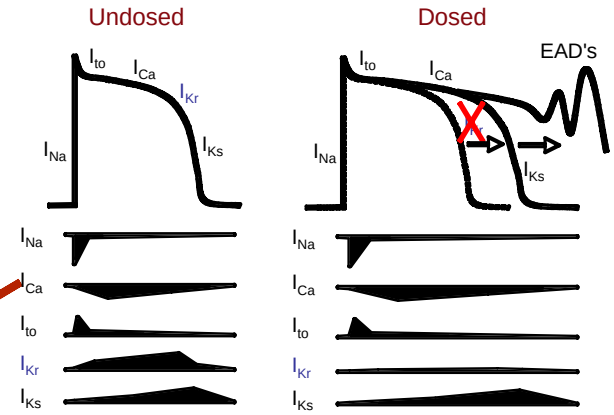
Action Potential

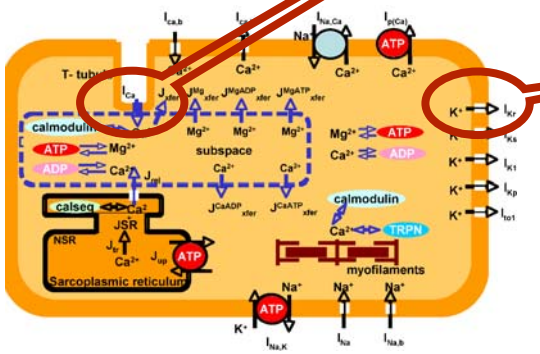


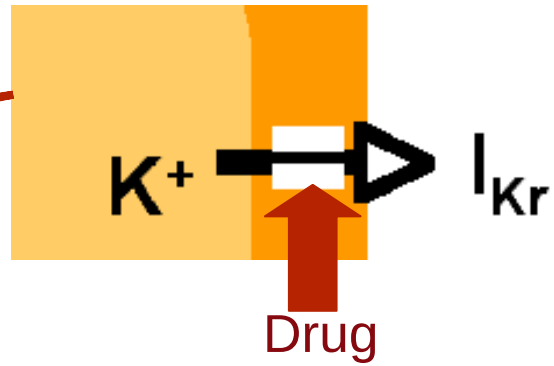
ECG

How does a drug affect action potential?

- The model integrates time dependent ionic fluxes - Na^+, K^+, Ca^{2+} - into a net current and its corresponding action potential
- Ion channels may be :
  - inhibited by drugs
  - modified by channel mutations

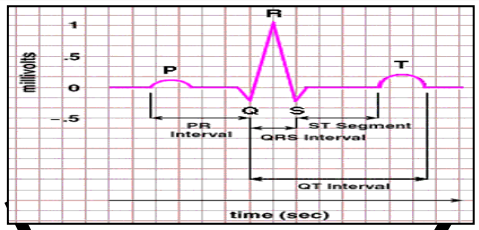


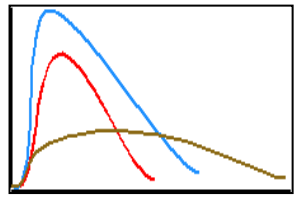




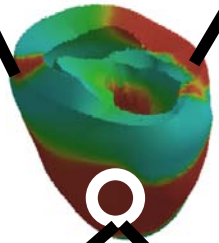
The *Systems Biology* view of drug induced cardiac liability

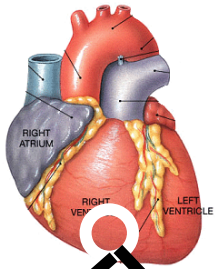
ECG, QT Prolongation?



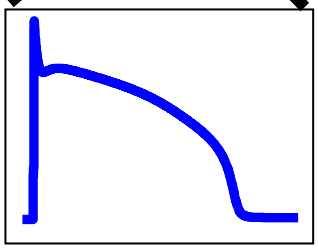


Excitation Propagation

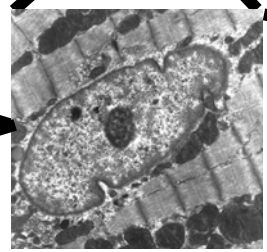




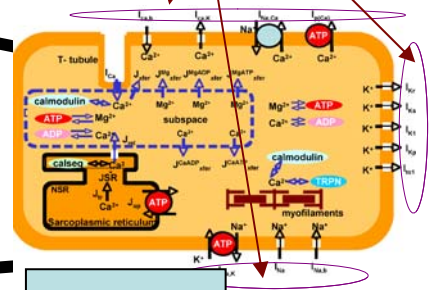
Drug MOA on channels



Action Potential



Myocyte



Myocyte

Mechanistic understanding of cardiac liability

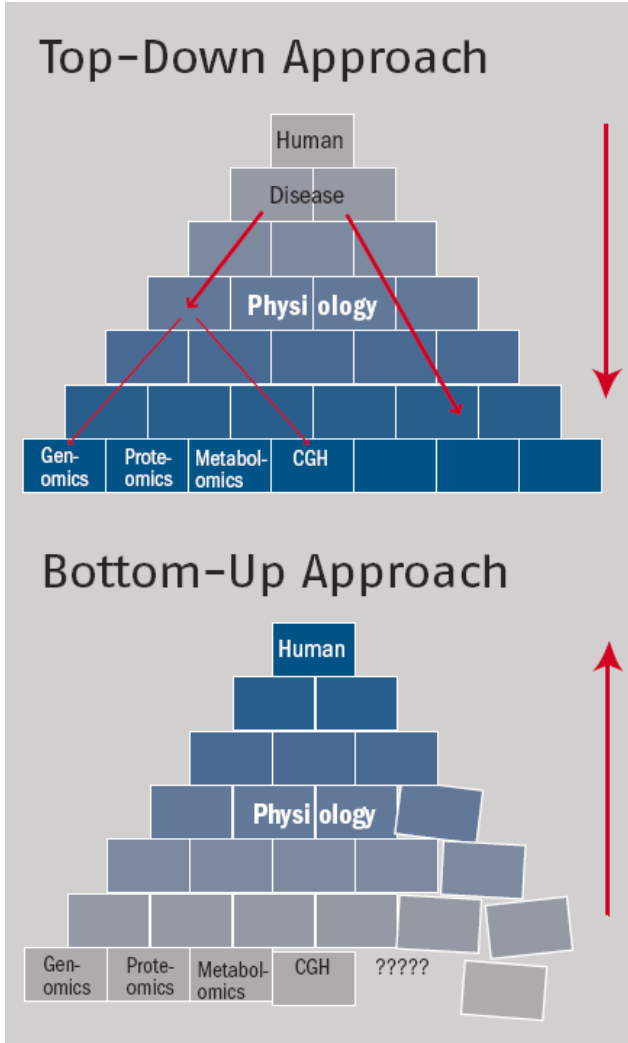
- QT prolongation alone is a very poor marker:
  - can be prolonged without arrhythmia, can be shortened with arrhythmia
  - all combinations are possible
- hERG also a poor marker:
  - I_{Kr} block could be part of a multiple action therapeutic agent
- Arrhythmia would be a better marker
- Virtually all the ion channels involved in cardiac repolarization are now modeled
- Very realistic simulations of the T wave of the ECG obtained when these models are incorporated into 3D cardiac tissue models
- Need to understand and predict arrhythmic mechanisms all the way from the molecular events at individual channels to the clinical outcome level of the ECG
- Thus need for systematic modeling at tissue and organ levels
- ***In silico* screens for drug development are becoming possible!**

Conclusions

Pathway and modeling interest in the pharmaceutical industry from the molecular to the organ level.

<u>Impact of computational systems biology:</u>

- Biomarker discovery
- Hypothesis generation
- Mechanism of action
- Improved decision support
- Adverse events prediction

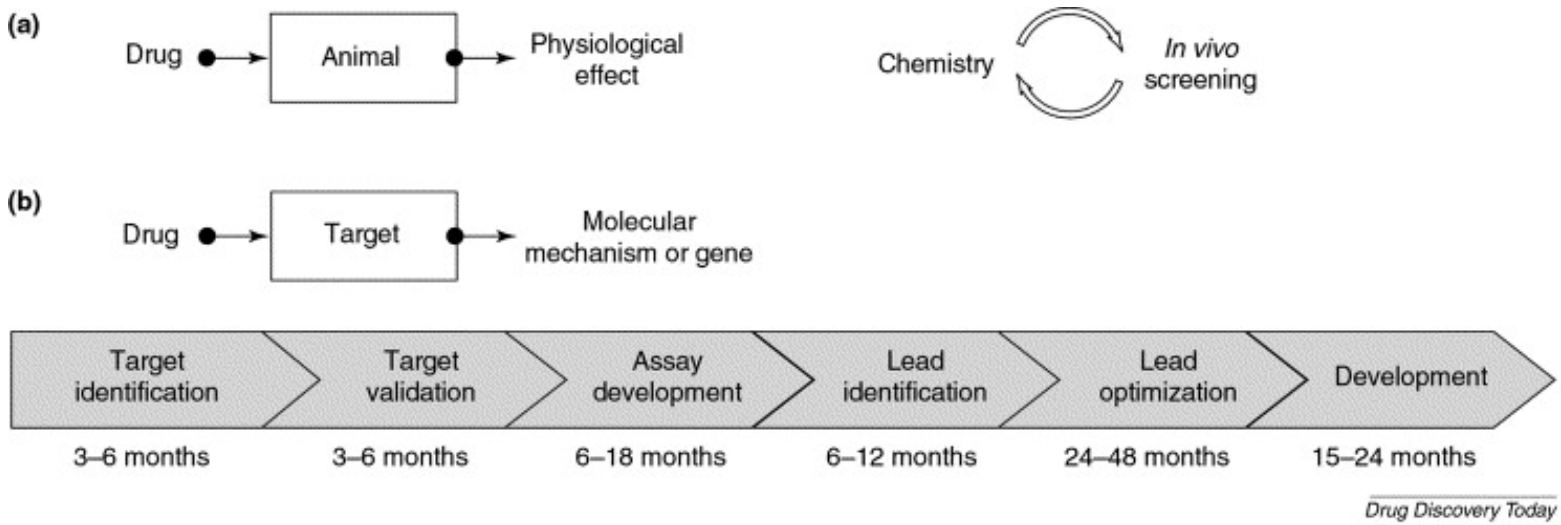


Acknowledgments

- Feby Abraham
- Valeriu Damian-Iordache
- Pankaj Doshi
- Chetan Gadgil
- Laura Potter
- Serge Dronov
- Hugh Spence
- Frank Tobin

Backup slides

Physiology- and target-based drug discovery



Dynamic models of ErbB signaling

- Prediction that kinetics of ErbB1 phosphorylation are defined by interactions of the receptor with adaptor proteins, which mask receptor phosphotyrosines from dephosphorylation
  - Kholodenko *et al.* (1999) *J. Biol. Chem.* **274**:30169.
- Two-compartment implementation of receptor internalization, and Shc-dependent and Shc-independent signal transduction of MAPK activation.
- Binding affinity of ligand defines signal efficacy, by governing the initial velocity of receptor activation, which potentially explains the utility of EGF-ligand multiplicity.
  - Schoeberl *et al.* (2002) *Nature Biotechnol.* **20**:370.

Dynamic models of ErbB signaling

- Models for receptor trafficking
  - Resat *et al.* (2003) *Biophys. J.* **85**:730.
  - Maly *et al.* (2004) *Biophys. J.* **86**:10.
- Non-intuitive observation through modeling of ErbB1 endocytosis:
  - High potency of a low-affinity mutant of EGF.
  - Mutant has a high mitogenic potential because of increased receptor recycling.
    - Reddy et al. (1996) *Nature Biotechnol.* **14**:1696.
- Another emergent feature of EGF signaling attributes to receptor endocytosis:
  - A protective effect at high ligand concentrations
  - But attributes a signal-amplification effect at low concentrations of EGF
    - Schoeberl *et al.* (2002) *Nature Biotechnol.* **20**:370;
    - Haugh & Lauffenburger (1998) *J. Theor. Biol.* **195**:187.

Theory gap for large systems

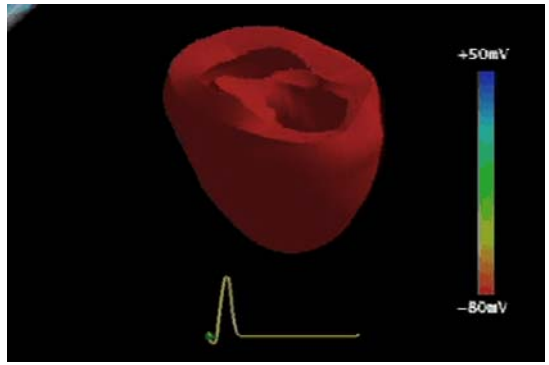
- Large but not infinite dimensionality is the problem
- Analytical and numerical determination:
  - Finding ‘true’ null states – there may be a great number
  - Finding linear null states – there may be a great number
  - Asymptotic behaviors
  - Controllability, predictability, integrability, …
  - Steady-state, non-linear behaviors
  - Bifurcation analyses
  - Perturbed behaviors – drug dosing, environment, mutants, etc.
  - …
- How to calculate in a computationally efficient manner
- Can’t afford to calculate everything
- Need to *a priori* determine which are to be done

Whole heart modeling: AP to ECG

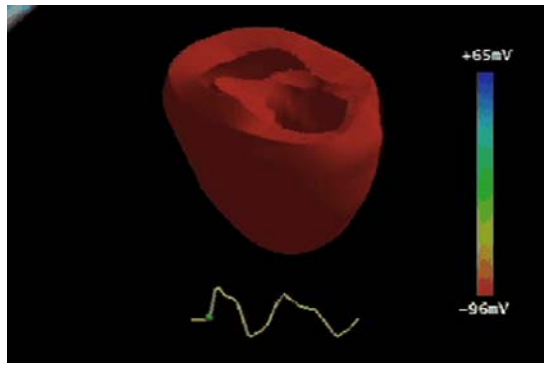
Whole heart model

- Built up from multiple copies of the myocyte models
- Electrical currents and ion concentrations propagated from one cell to the next over time
- Spatial and temporal current changes based on theory of excitable media
- Very expensive computation for just one heartbeat

Canine normal heart



Canine heart: Congestive heart failure



Ray Winslow, The Johns Hopkins University