An Adversarial View of Biological Communications

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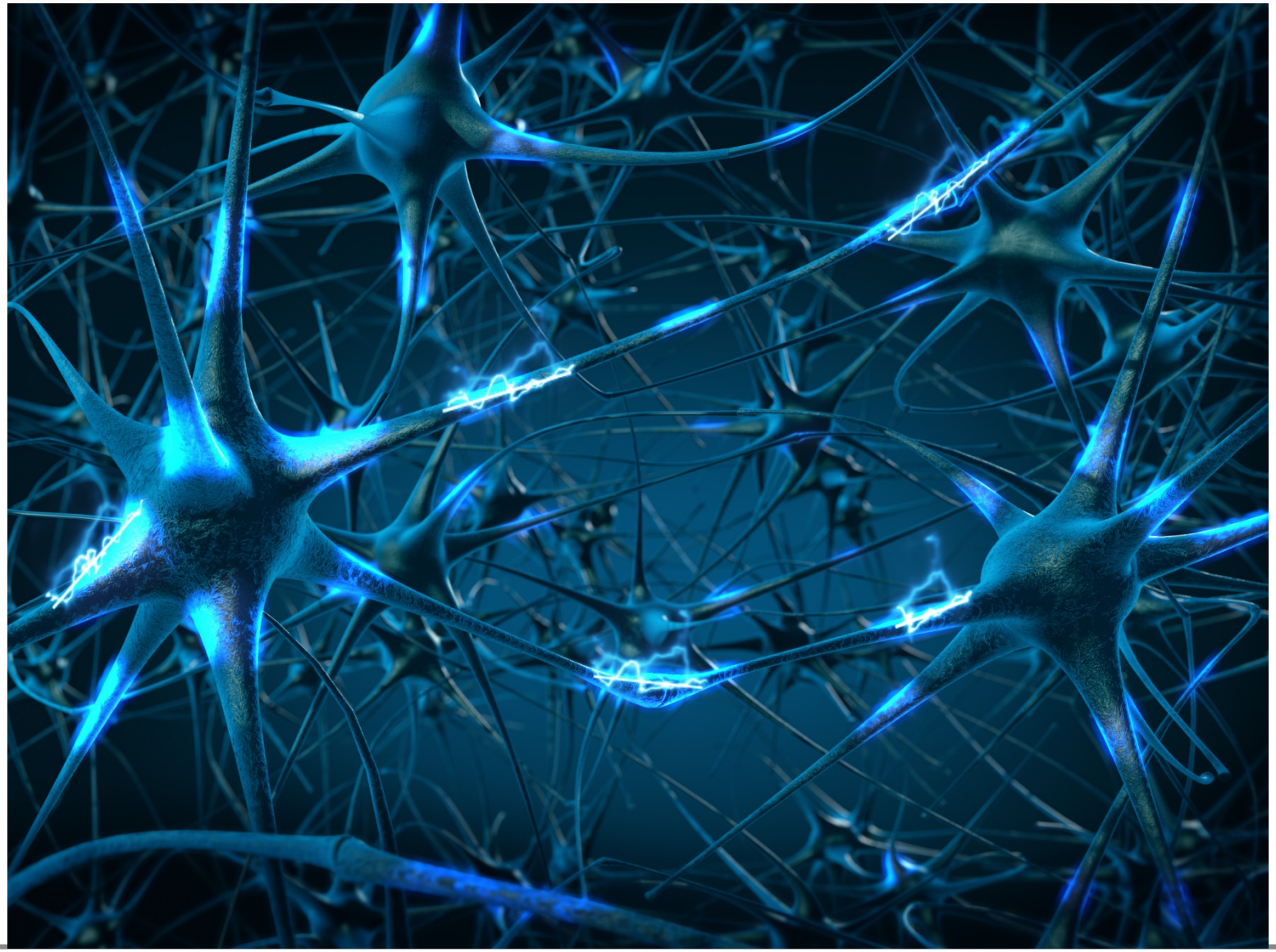
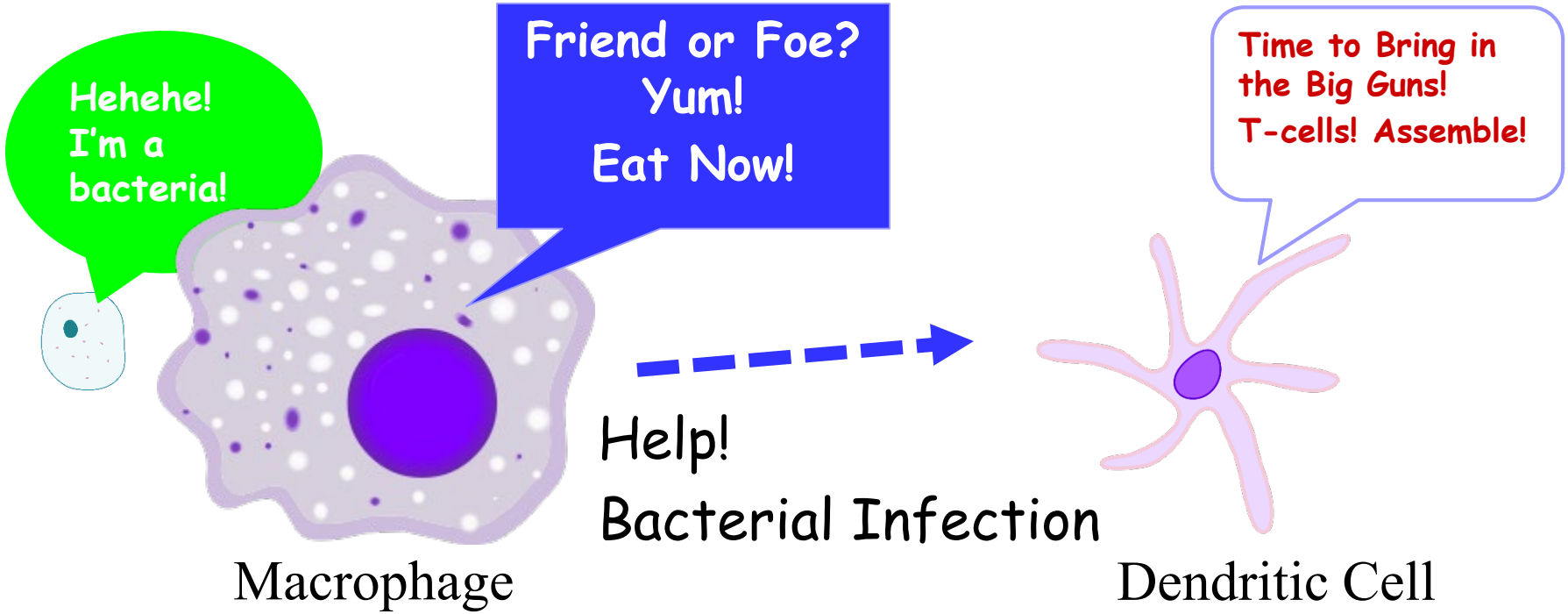
Through the Looking Glass: An effort to study how communications and biology meet.



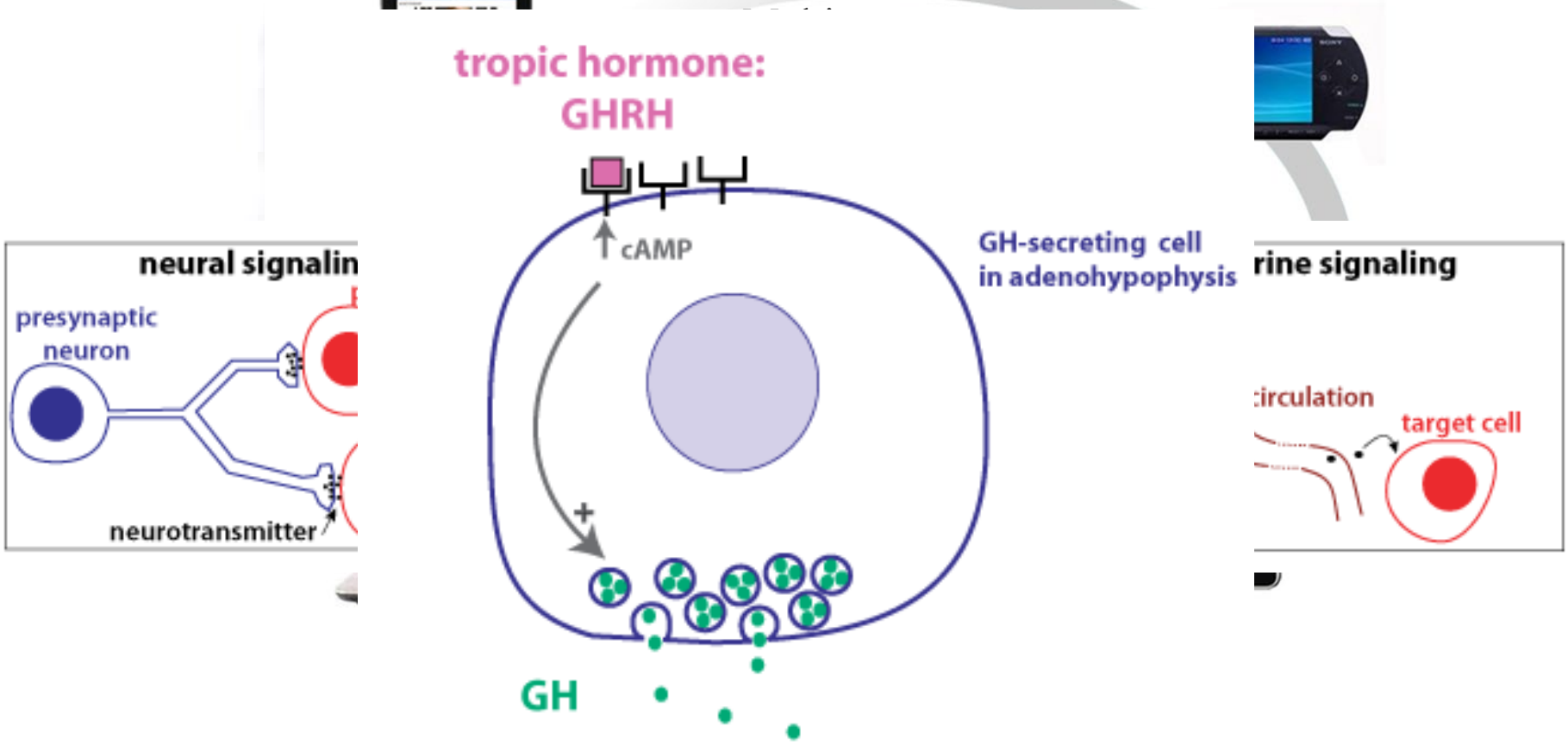
Starting Point: Biological cells need to communicate with each other



- Cells communicate with each other by the release and reception of extracellular signaling molecules
  - Hormones, cytokines, growth factors…
- Many extracellular signaling molecules are responsible for diseases (through their presence or lack of presence)
  - Cancers often hijack signaling mechanisms to control cellular functions

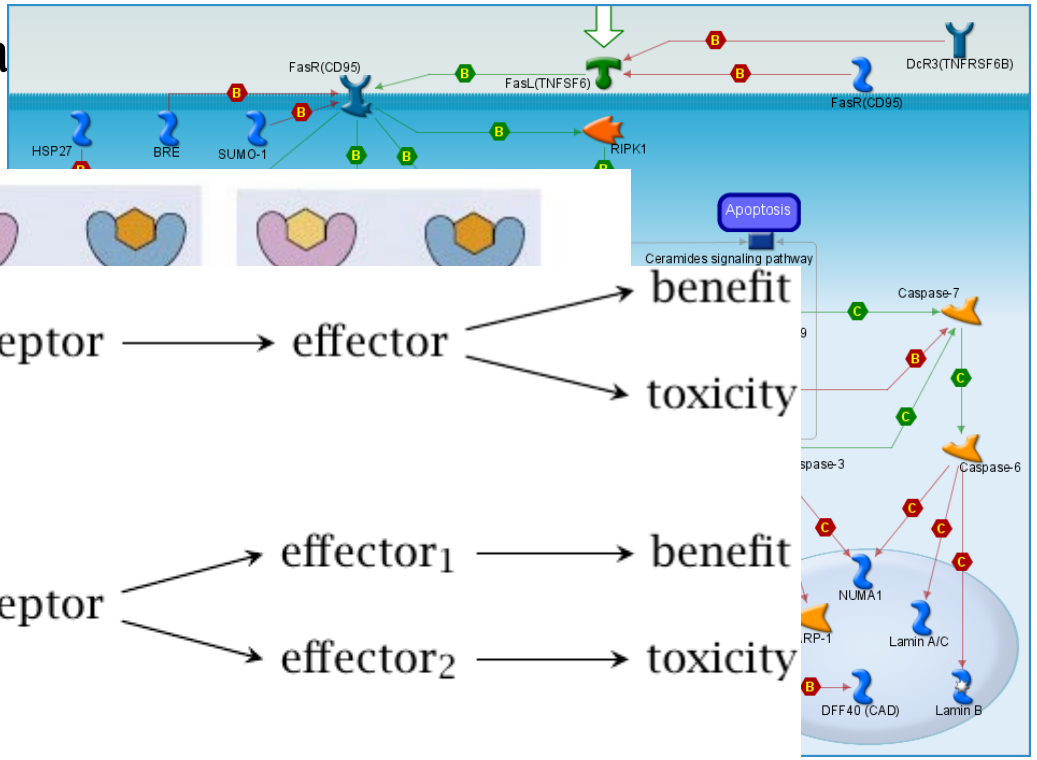
Parallels between our comm and bio-comm

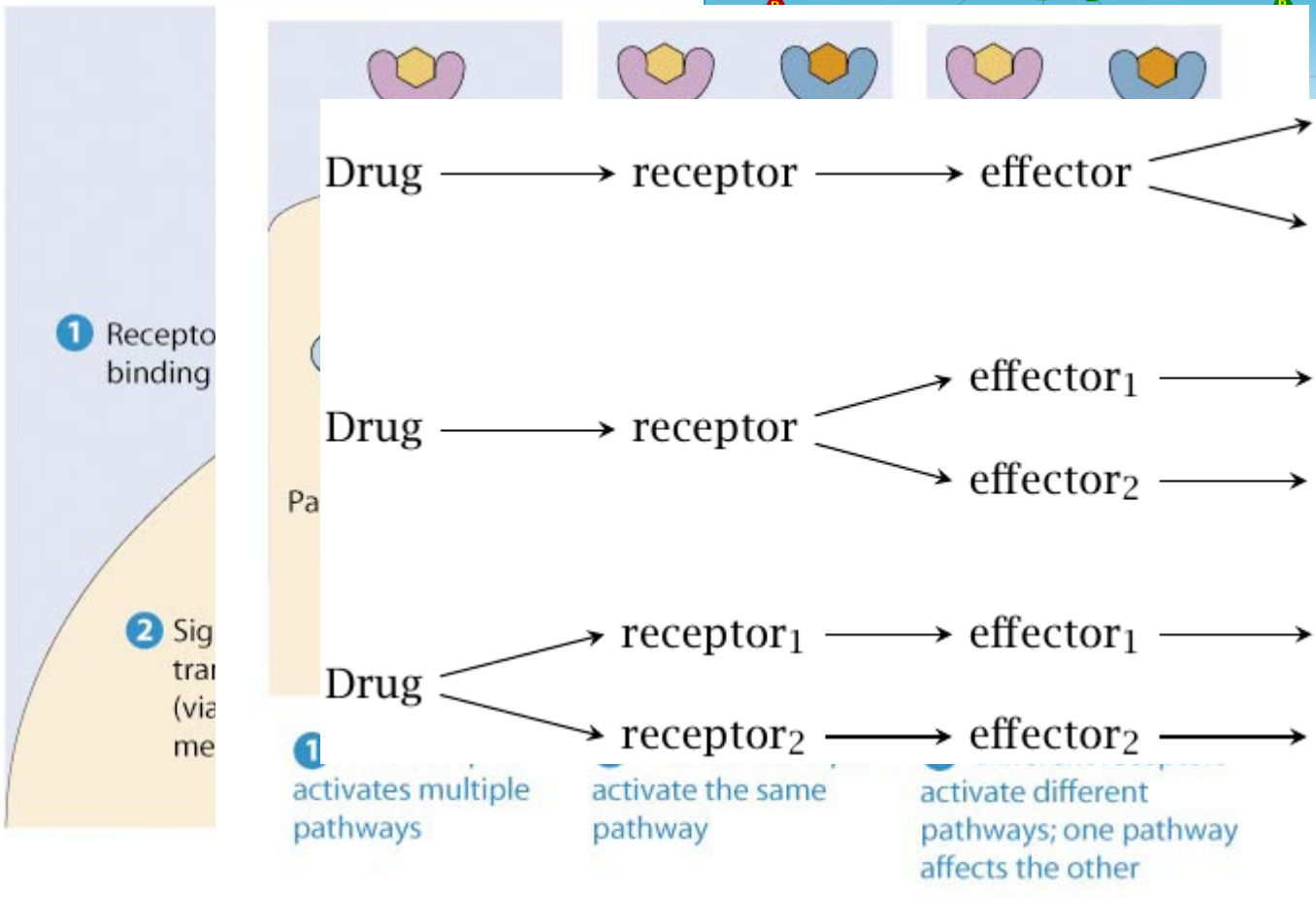
Broadcast



Targeting biological communications and signals is one of the tenets of medicine

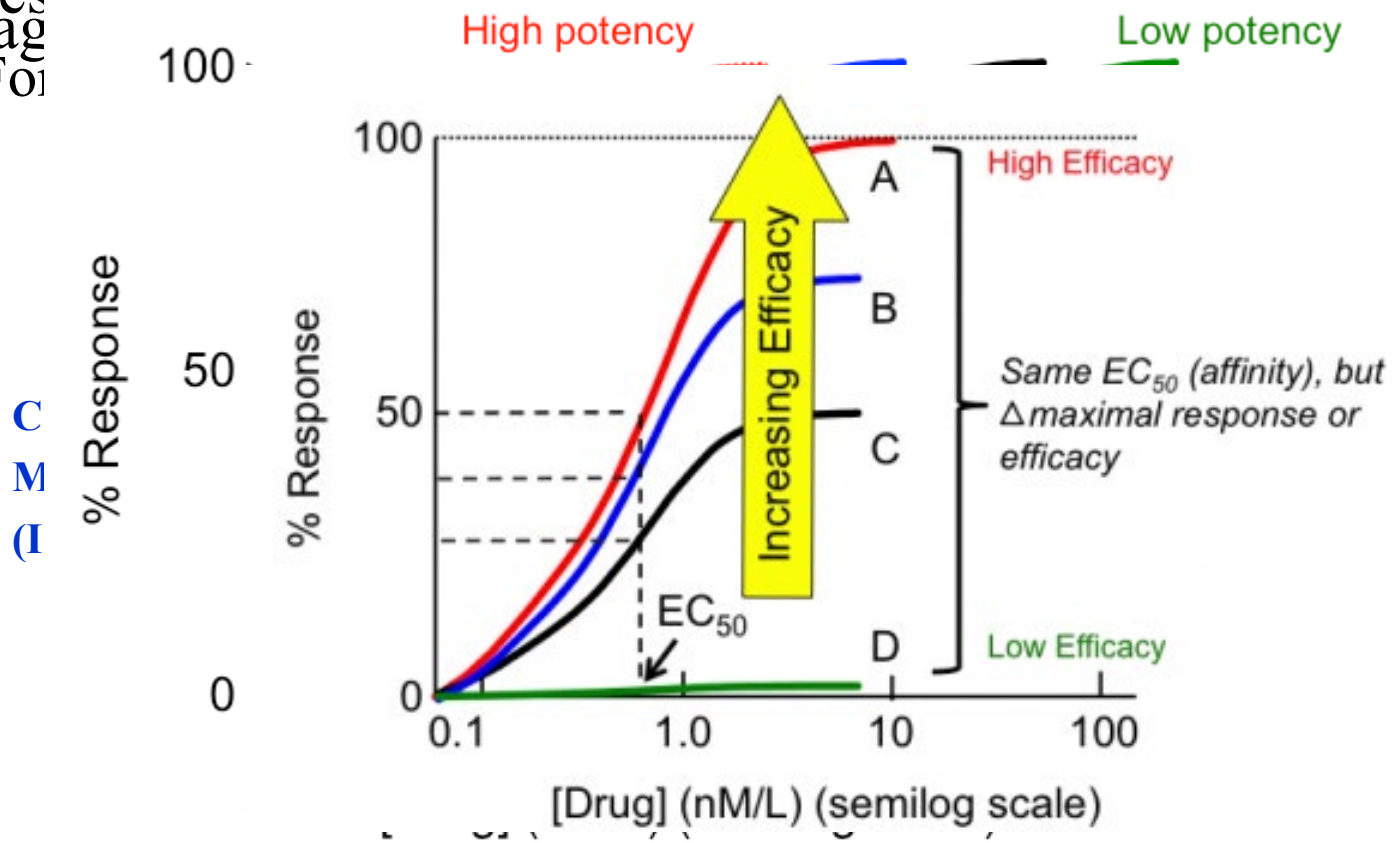
- One of the most importa
concept of a *receptor*.





Pharmacodynamics 101

- Modern medicine is about understanding how the human body reuses
- Agonists: Activate receptors to produce desired effect
- Antag
  - Fo



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- And now the bad news… you have toxic and lethal versions of these curves

"SNR"

Can we apply communications modeling to gain insight into biological functions?

- Communications tools allow for modeling problems like interference, competition between agents, resource assignment, tradeoffs, system interconnectedness, etc…
  - All of these are (almost) ideal tools try to tackle problems in biological systems and health
- Vignettes:
  - Beneficial versus harmful tradeoffs
  - Multiple drugs and therapies
  - Biological circuits are networks and require thinking like network engineers
  - Insights from control theorists…
  - How to tear down a network…

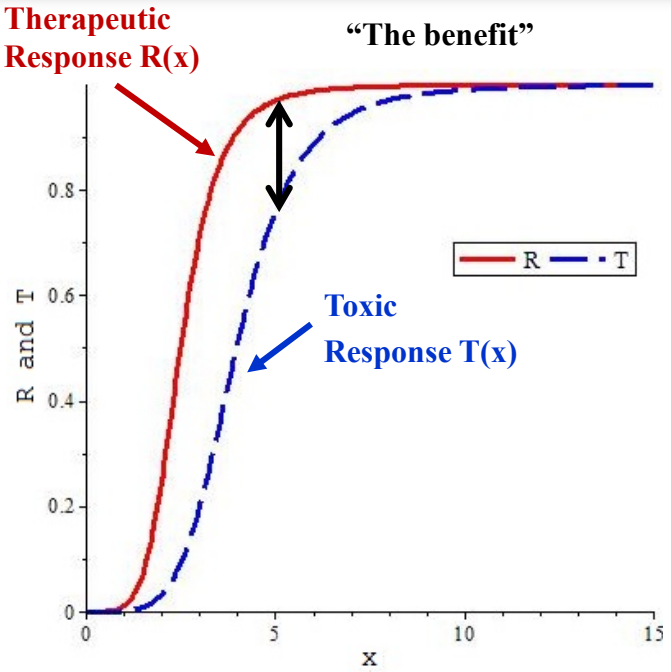
Resource Management and Bargaining in Pharmaceutical Dosing

- Pharmaceutical agents are characterized by therapeutic and harmful effects
  - Dilemma how to appropriately tradeoff between "good" and "bad"
  - Traditional pharmacology: population studies to determine population effective and tolerable dosages
- Possible to apply resource management as a framework to address this problem:
  - Analytical dose-response relationships (e.g. Langmuir, Michaelis-Menton)

$$R(x) = \frac{a_{max} x^n}{a + x^n}$$

$$S(x) = b_{max} - \frac{b_{max} x^n}{b + x^n}$$

  - Nash Bargaining Solution is unique, can be found explicitly, and maximizes the "safe treatment response"

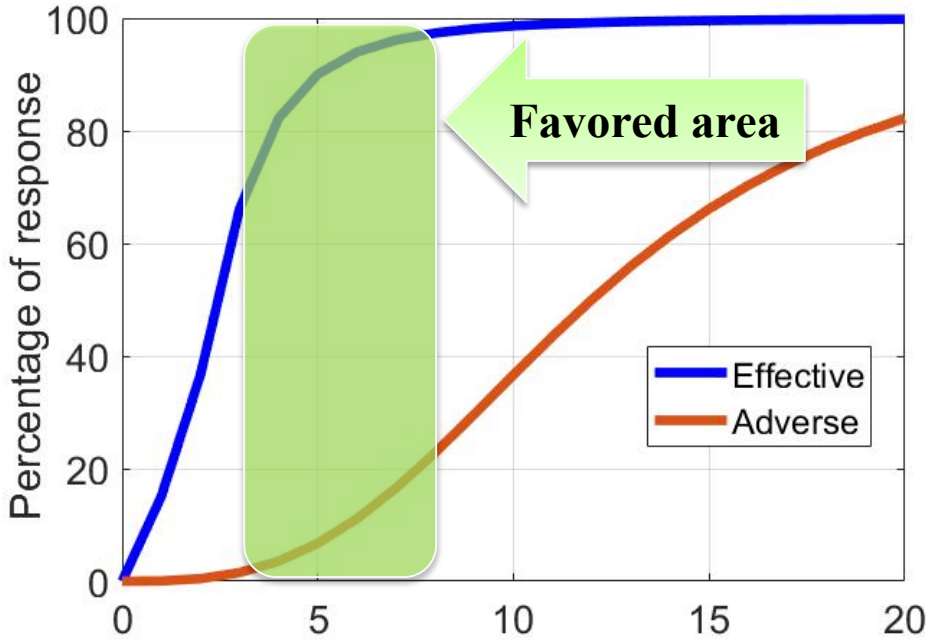


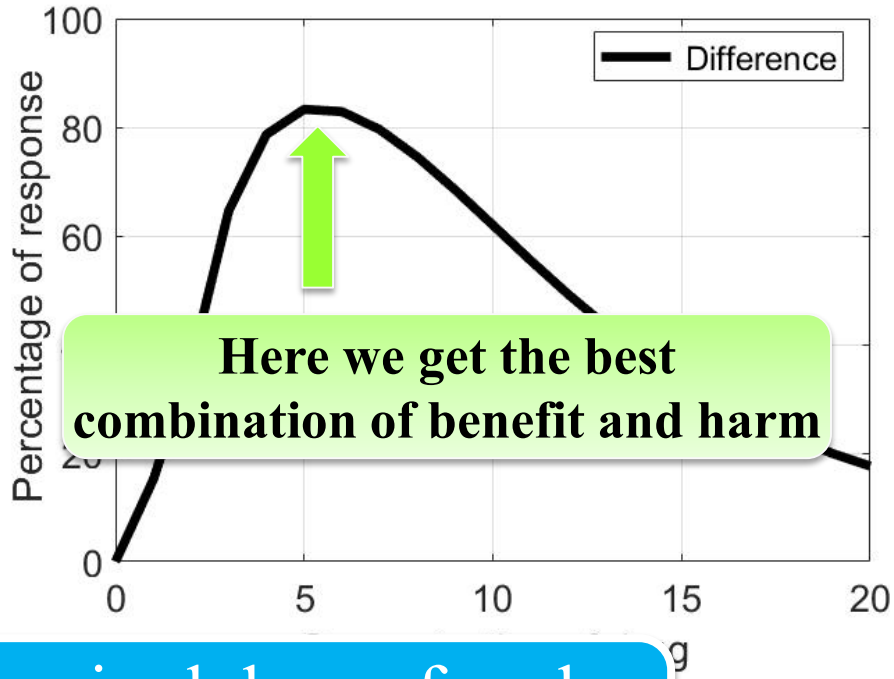
- Framework is modular: swap out cost functions easily (e.g. maximize response while addressing production cost)
- Extension to multi-drug combinations is being explored
  - Chou-Talalay combination index for receptor-based treatments

When cocktails of drugs are more effective than single ones; Migraines as an example

What do you take when you have a headache?

How can we find the opportunities to do more with less?





We can lower the required dose of each drug when used in a combination

How can different drugs benefit each other?

Multiple dr
benefits, if
blem

Cancer and many other diseases involve many different factors and if we can hit the disease on different fronts, then we have a hope to combine drugs to tackle this problem.

Migraine: AAC

(250 mg acetaminophen/250 mg aspirin/65 mg cafeine)

Cancer and

Cancer and signaling
ys

HIV: Atripla

(600 mg efavirenz/200 mg emtricitabine/300 mg tenofovir DF)

A tumor consists of a genetically diverse population
of cells. A single
a portion of the
more likely to le
ts through
nvestigate
hin
tworks.

Cancer:

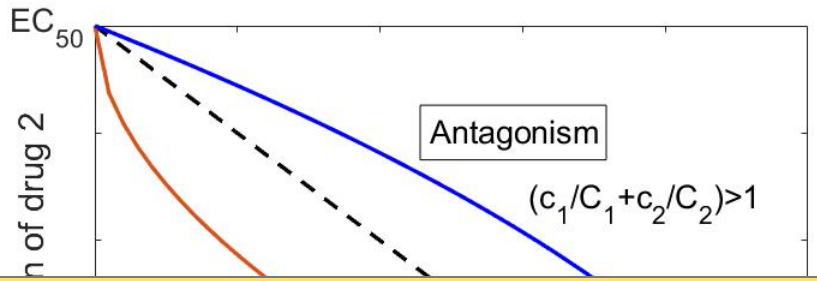
Thyroid: (dabrafenib + trametinib) *

Kidney: (avelumab + axitinib) **

certain w

- * https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm606165.htm
- ** https://www.sciencedaily.com/releases/2019/02/190217115910.htm

How do combining drugs interact with each other?



Given the vast amount of possible combinations involving multiple drugs and the restrictions in time and resources, mathematical methods are helpful to model the interactive behavior of the drug mixture and the target.

Concentrations of the drugs that produce the same amount of effect as the combination, when they act as single drug

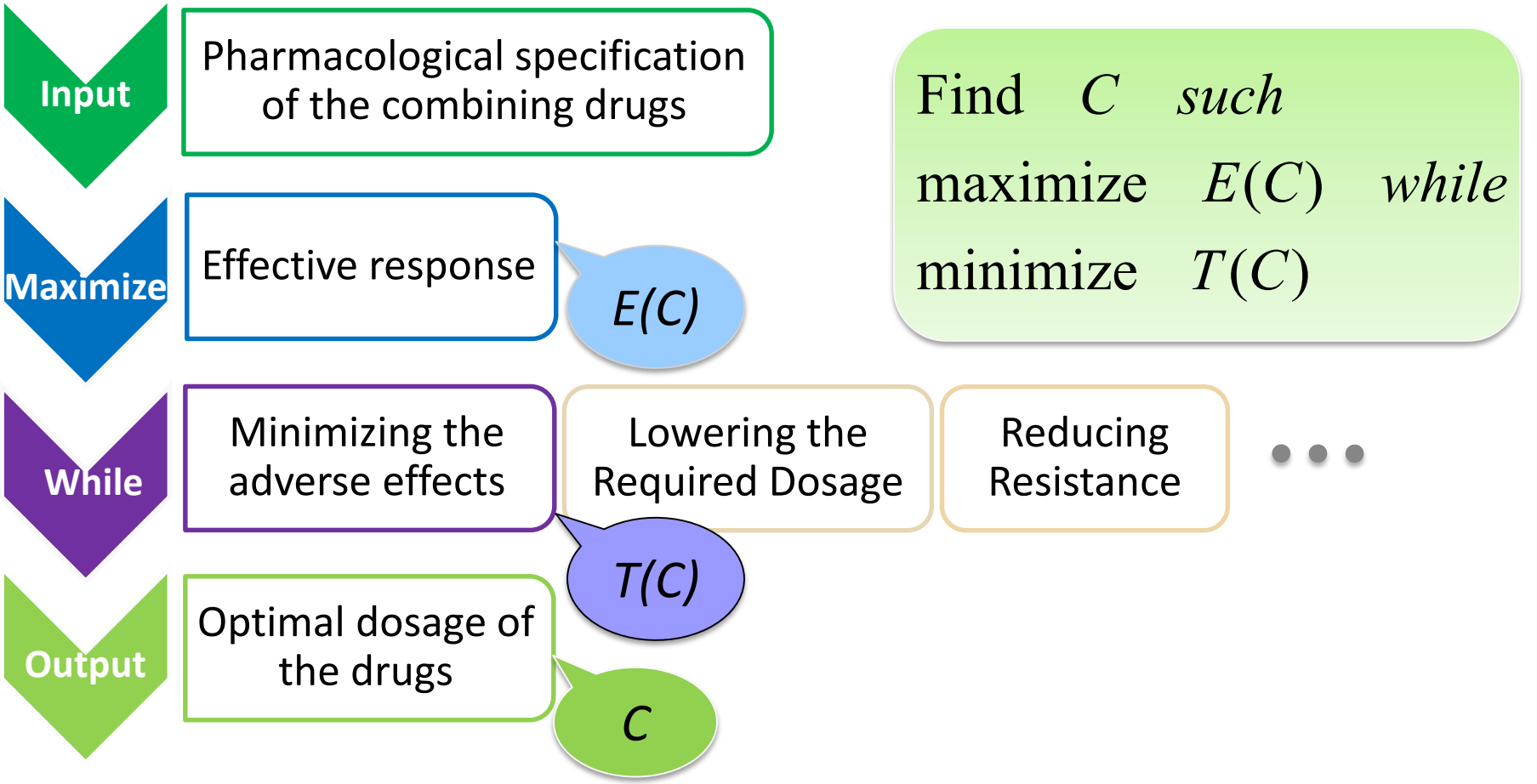
optimization tools

Non-interactive

Synergistic

Antagonistic

How do we determine the optimal doses in combination therapy?



When to use what for which scenario?

There are different models in applied pharmacology

Median-Effect

$$E_i(c_i) = \frac{c_i^{n_i}}{M_i^{n_i} + c_i^{n_i}}$$ ← Fractional affected

$$U_i(c_i) = \frac{M_i^{n_i}}{M_i^{n_i} + c_i^{n_i}}$$ ← Fractional un-affected

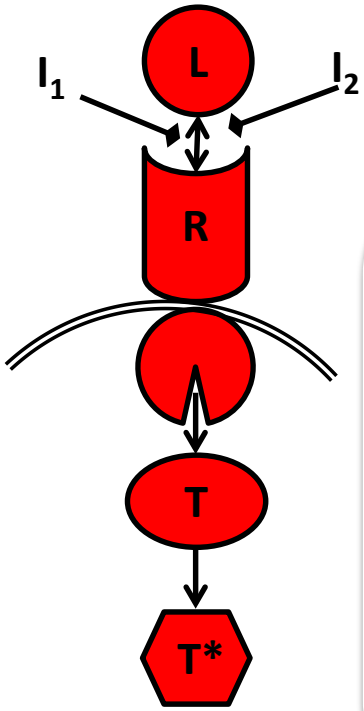
$$\left(\frac{\mathbb{E}(\mathbf{C})}{\mathbb{U}(\mathbf{C})}\right)^{1/n} = \sum_{i=1}^{N} c_i - \sum_{i=1}^{N} \left(E_i(c_i)\right)^{1/n}$$

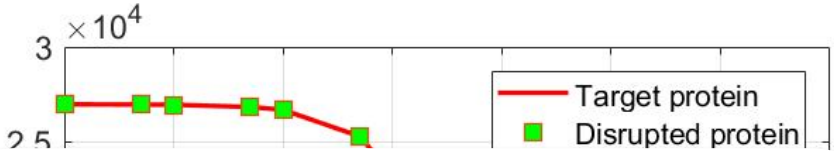
Mutually exclusive agents with

$$\mathbb{E}(\mathbf{C}) =$$

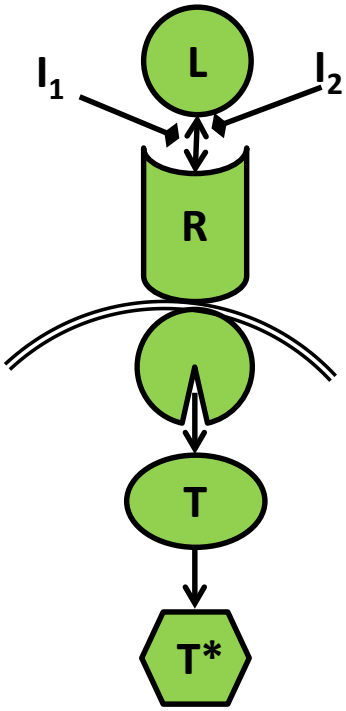
The conventional methodologies, which are based on dose-effect models, do not reflect the dynamical behavior of the disease's "network"

Avoiding mechanism-based toxicity in signaling pathways by optimizing drug combinations





If there exists another inhibitor with less (and different) effect on the healthy pathway, then the optimal combination of two inhibitors could be found that blocks the targeted protein with less effect on the healthy cells

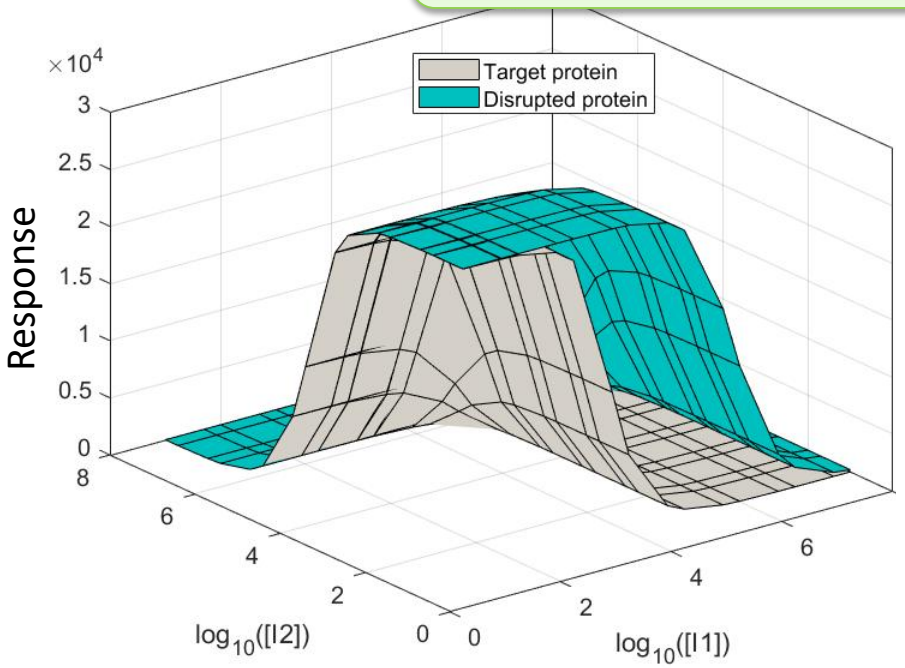


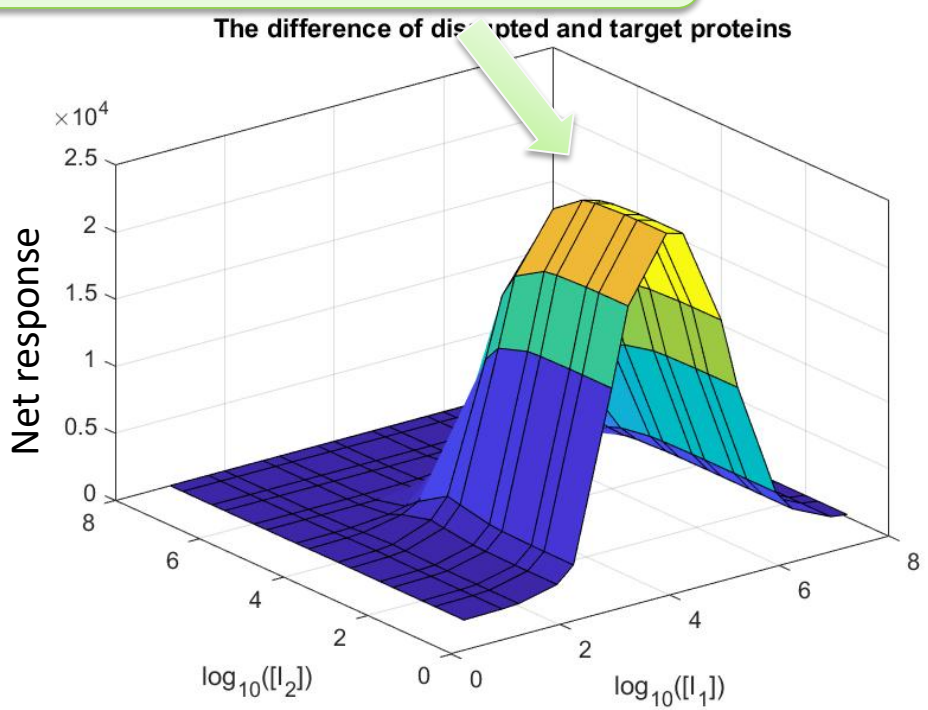
Target pathway

Unintended inhibited pathway

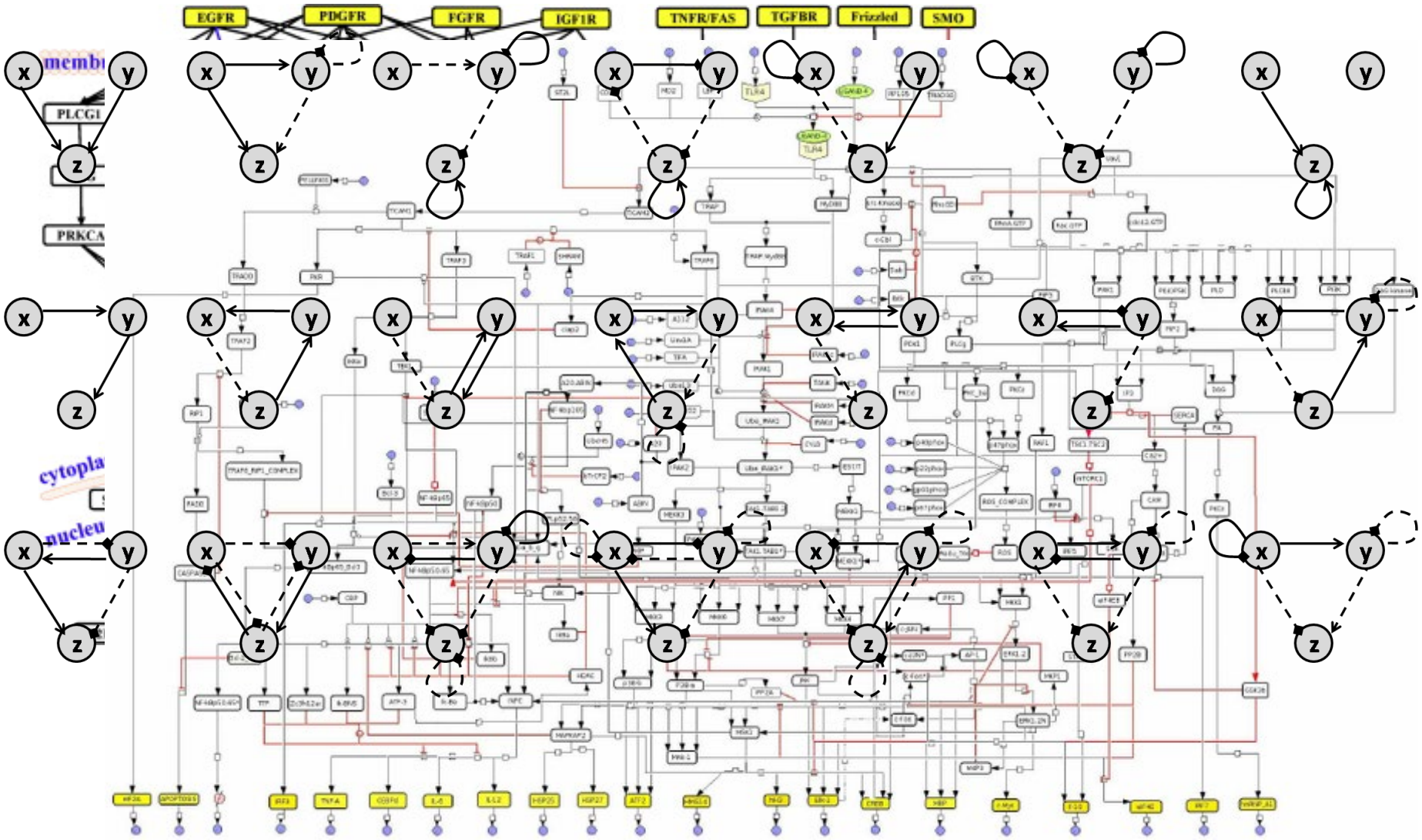
The pathways respond to the combination of two inhibitors differently

Here we get the most blockage on the intended and the least impact on the unintended inhibited pathway





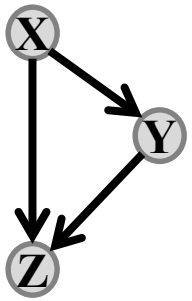
Understanding the network of connections and interactions is the basis of network pharmacology



Diagrams from Wu et al., Journ. Taiwan Inst. Of Chemical Engineers 2014; M. Padwal et al. PLOS ONE 2014 ; V. Vakil and W. Trappe, Pharmaceutics 2019.

Adversarial Modeling and Disrupting Biological Circuits

- Biological systems are complex with many interacting components or agents
  - Many examples of metabolic, genetic, transcription, and protein interaction networks within and among cells
  - Interaction networks are often simplified using network motifs



The Feedforward loop in which signals from X activate Y and Z.

Upon activation Y emits signals to coactivate Z.

X aims to activate Z through combination of direct and indirect paths.

- X may portion out cytokinens to primary and secondary paths of the FFL.

$$\boldsymbol{P} = (P^P, P^S)$$

$$p^{XZ} = 1 - e^{-\alpha SNR(\boldsymbol{P})}$$

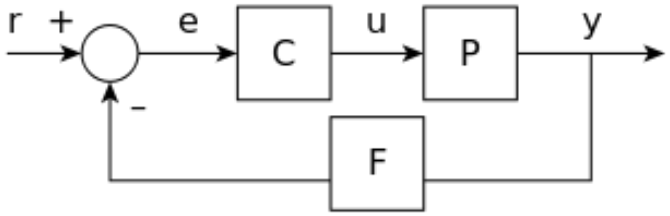
$$v(\boldsymbol{P}) = p^{XZ} + p^{XZ}p^{XZ} - p^{XZ}p^{XY}p^{YZ}$$

  - We may aim to maximize $v(\boldsymbol{P})$ subject to resource metabolic constraints (aka "resource constraints")
  - Framework allows one to introduce penalties to indirect path (e.g. Y→Z cytokinen might be used in another pathway)

- Framework also allows us to introduce an "adversary"
  - Can introduce a pharmacologic agent to disrupt the effects of X→Z, X→Y, and Y→Z legs of the FFL
  - Analagous to introducing a jammer
- Jammer agent may allocate its resources against X→Z and X→Y paths
  - Game theoretical models may be applied to understand the competition between "nature" and "the doctor"

Feedback: Robustness and bistability

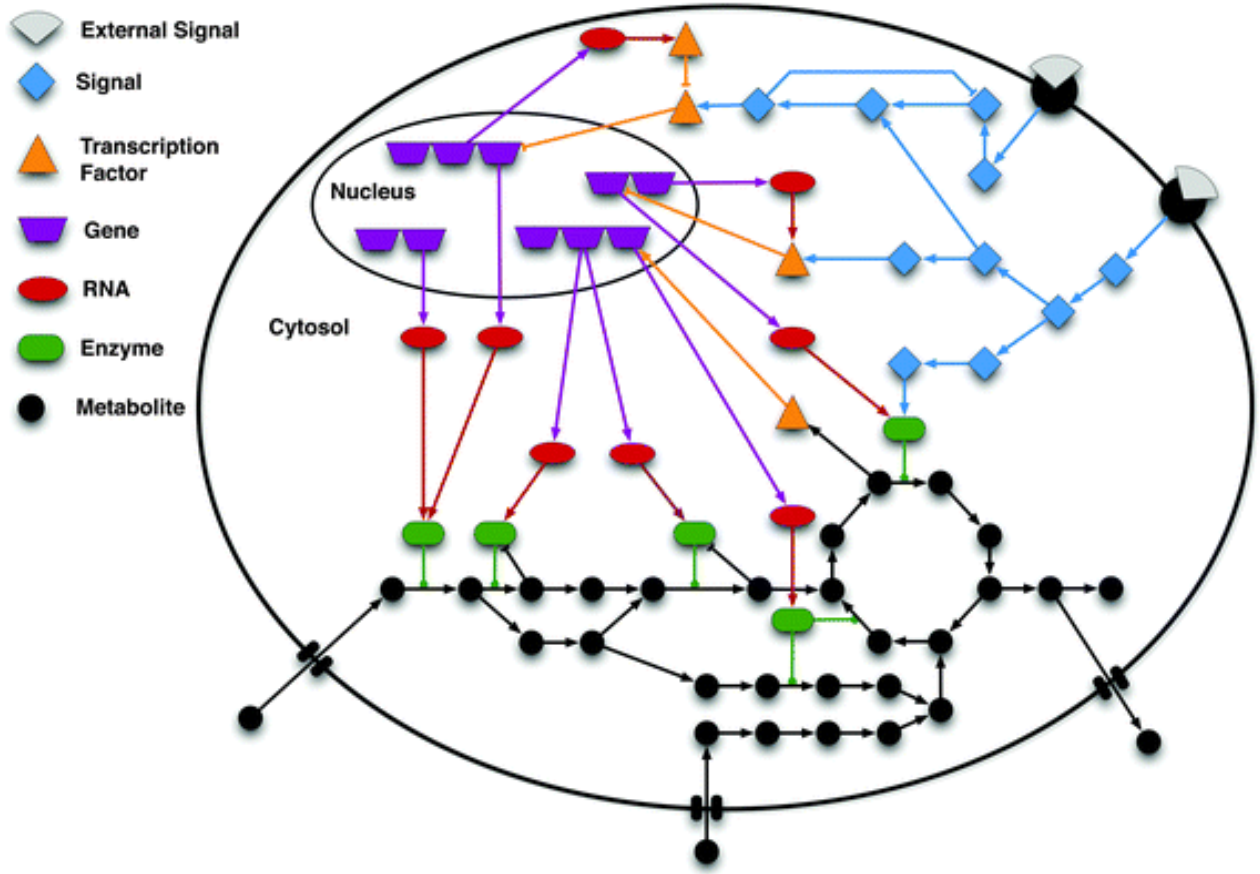
- Feedback is very has common in biological systems
- Feedback has numerous advantages
  - Decreased sensitivity to variations in parameters
  - Rejection of disturbances and noise attenuation
  - Reduction of steady-state error in system objective
- Drawback: potential instability if feedback takes too long or corrects too strongly
  - Autoimmune diseases



- Negative feedback is generally resilient
  - Implication for drug targeting: Don't target the process "in the loop"
  - Target reactions outside the loop
- Positive feedback can generate bistability
  - Allows for a system to self-rectify degraded "signals"

How to target the network?

- Network interdiction: [illegible]
  - Formulate the adversarial battle as a "fitness" game with rewards and equilibria, and try to alter/control the equilibria (3rd players)



Diagrams from E. Goncalves et al., Molecular BioSystems, 2013.

Conclusions

- Biological systems are inherently communication systems
- We are aiming to apply tools from communications and "disrupting communications" to better understand medical treatments
- Many fantastic, complicated examples abound in the real world:
  - Quorum sensing and bacteriophages+lysis
  - Cancer immunogram (tumor foreignness, hypoxia, fibrosis)
  - Three players worse than 2, but four players might be better than both…
- Multifaceted, multi-pronged approaches necessary for personalization
  - Biomarkers and patient-level differentiation essential to personalizing and optimizing treatment
  - Better "quantitative" data is needed for personalizing treatments