

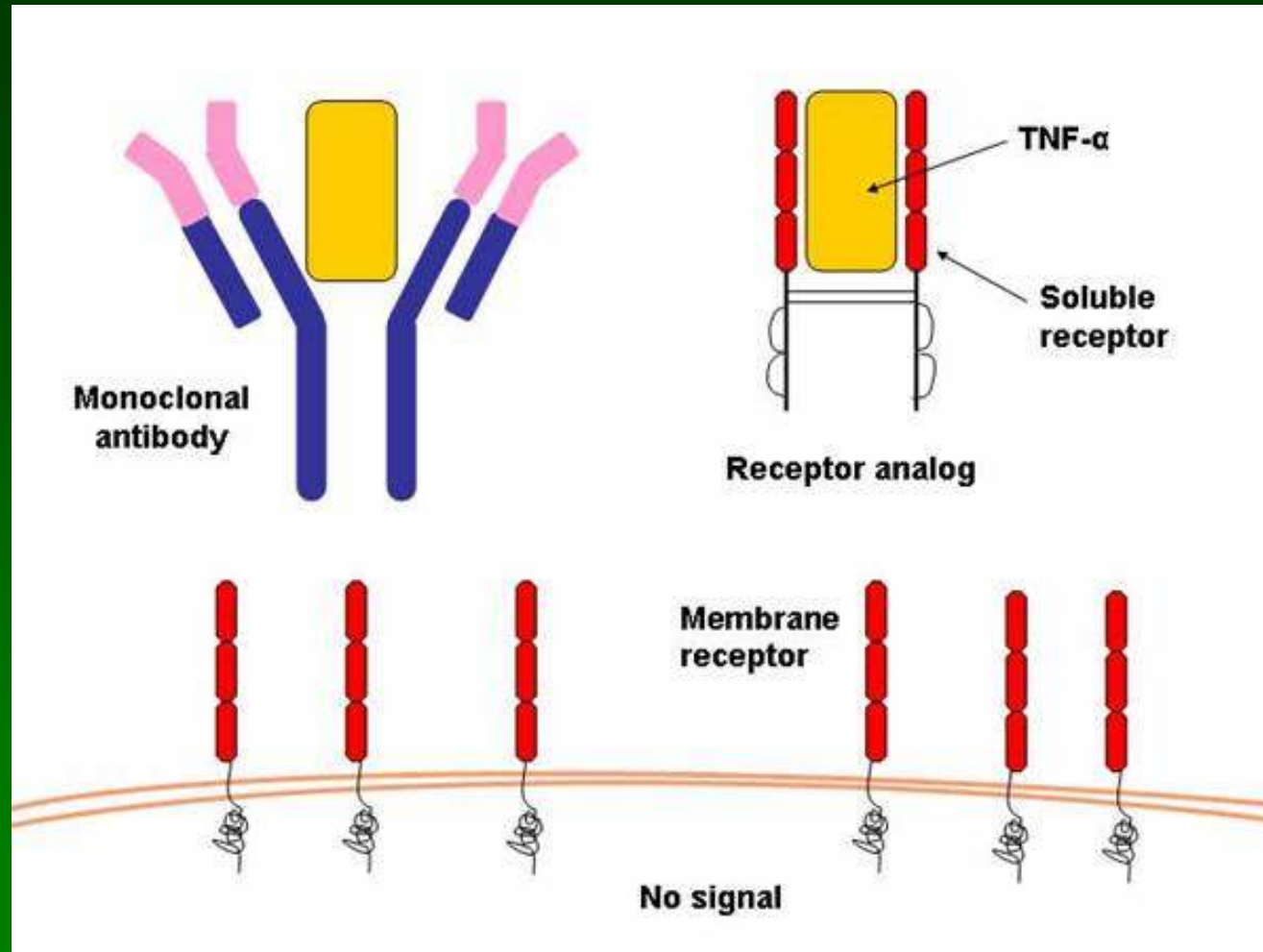
A Mathematical Model to Explain the Differential Clinical Effects of TNF- α

Student: Cyndi Trevisiol
Mentor: Tarynn M. Witten

Outline

- **Jit M et al. 2005, TNF- α neutralization in cytokine-driven diseases: a mathematical model to account for therapeutic success in rheumatoid arthritis but therapeutic failure in systemic inflammatory response syndrome, *Rheumatology*, 44(3): 323-331.**
- **Background**
- **An important question**
- **The model and the reasons it was used**
- **Meaning of the model's behavior**
- **Take home message**

Neutralization of TNF- α



Therapeutic Use of Neutralization

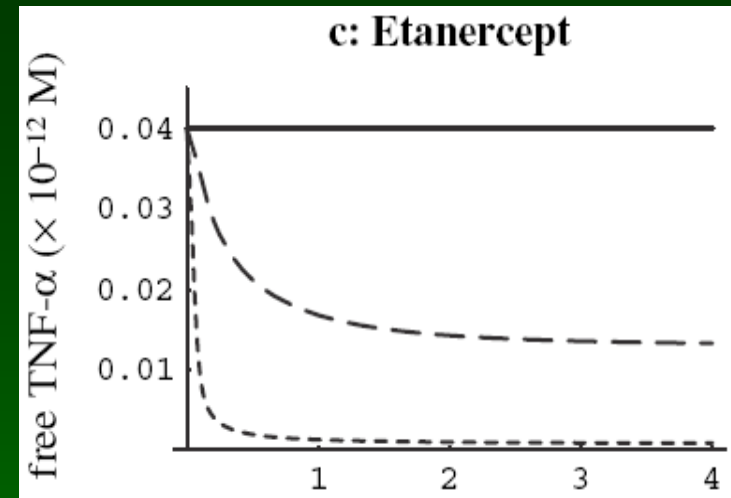
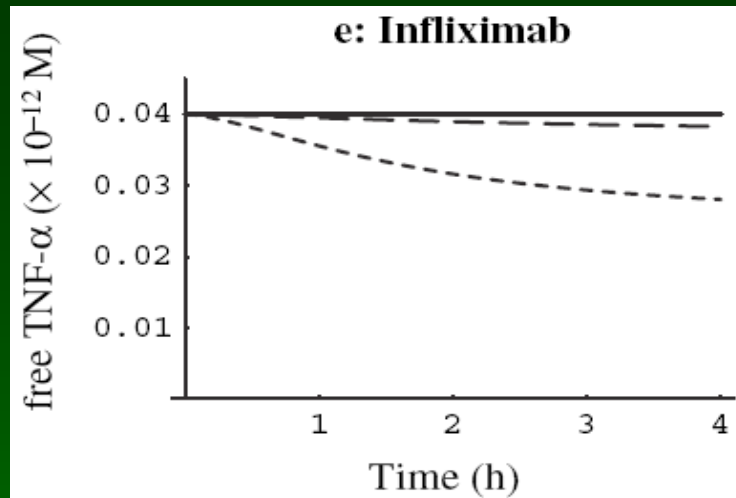
- **Rheumatoid Arthritis**
 - Chronic inflammation
 - Binding active TNF- α improves condition
- **Systemic Inflammatory Response Syndrome (SIRS)**
 - Uncontrolled inflammatory response
 - No response to neutralization in clinical trials

**Why the different
effects?**

Mathematical Modeling: Good for Dynamic Systems

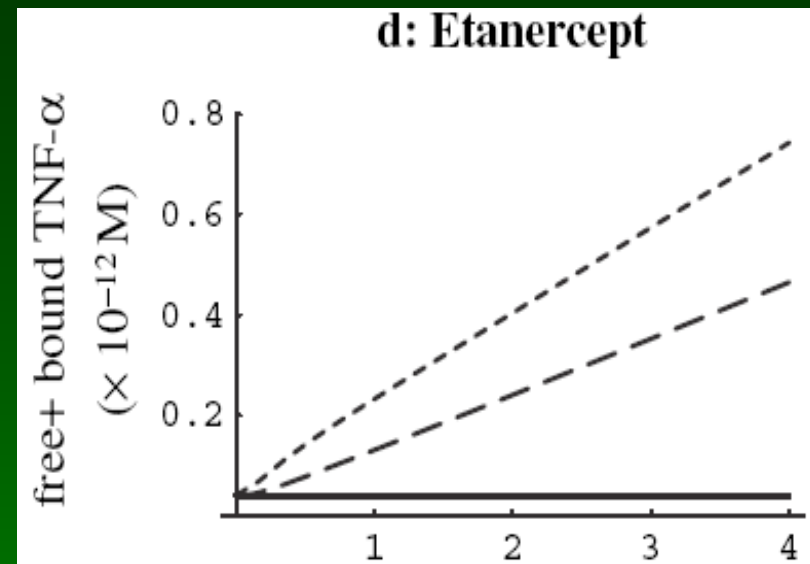
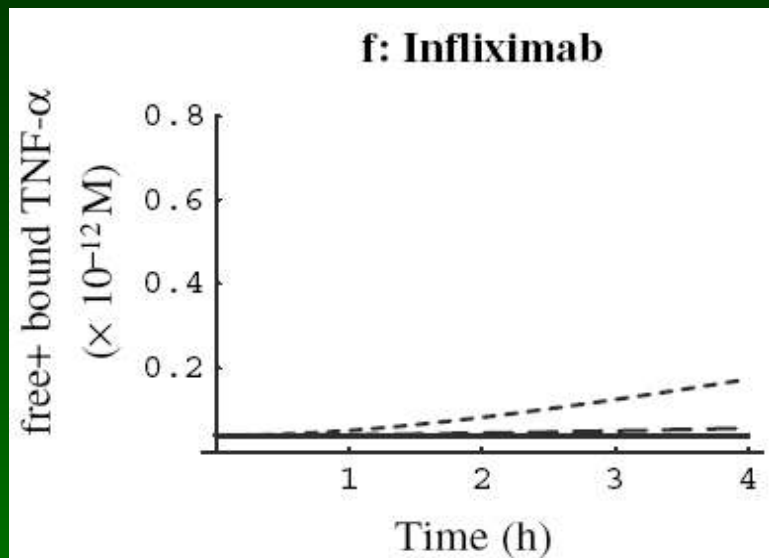
- Interactions between receptor, ligand, and inhibitor
- Nonlinear differential equation model
- Used published kinetic parameters for two inhibitors:
 - Infliximab
 - Etanercept

Model for Equilibrium Behavior



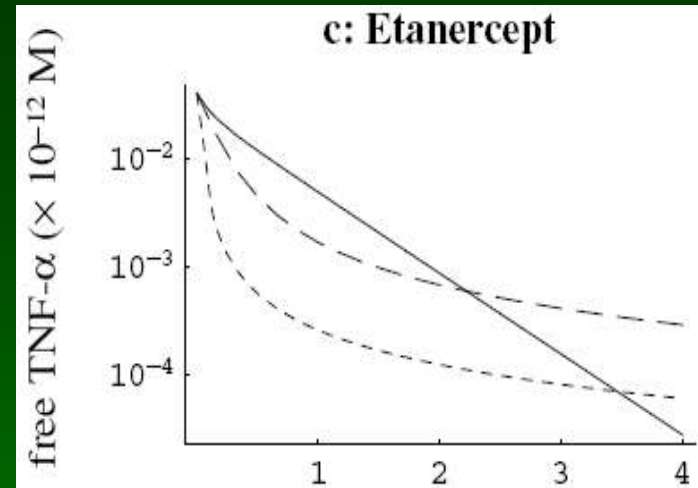
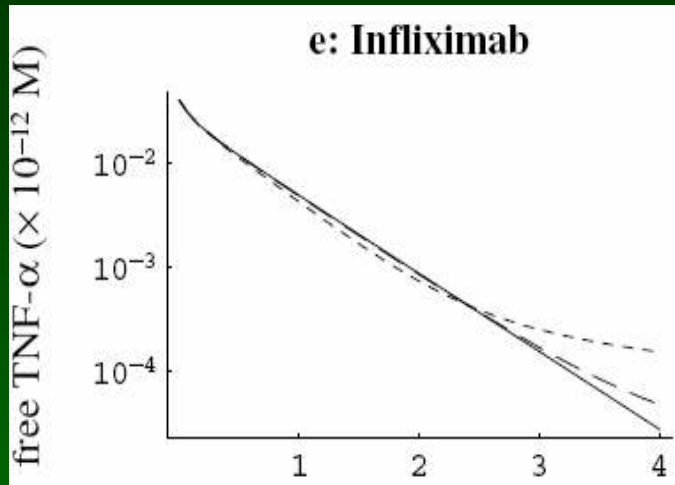
(Rheumatoid arthritis model)

Total TNF- α Over Time



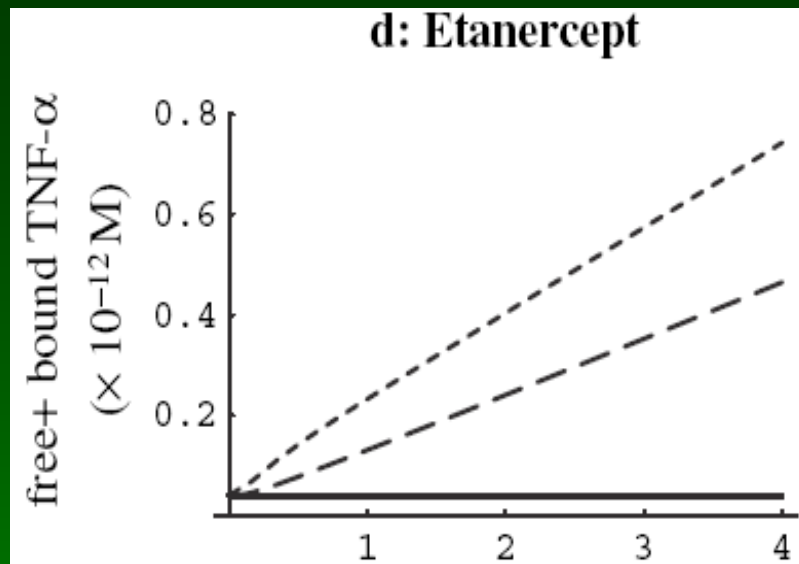
**Inhibition leads to an increase
in total TNF- α**

Model for Non-Equilibrium Behavior

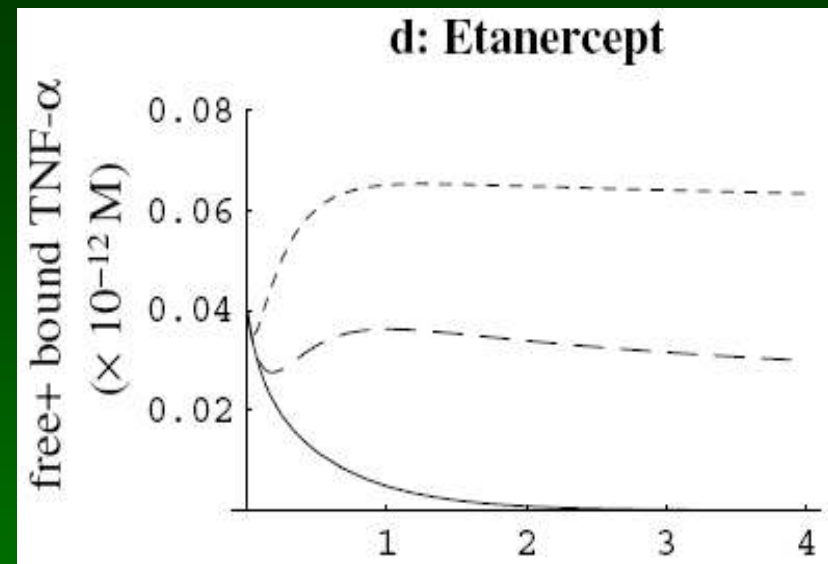


(SIRS model)

Comparing Total TNF- α Over Time



**(Rheumatoid
arthritis model)**



(SIRS model)

Take Home Message

- **SIRS is a non-equilibrium condition**
 - Over time inhibitors act as slow release reservoirs of TNF- α
- **Rheumatoid arthritis is an equilibrium condition**
 - anti-TNF therapies are a success
- **Success or failure of therapeutic agents is dependent on dynamic interactions**

Thank you for coming!