

# Biotechnology and Computational Biology

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MITRE Sponsored Research

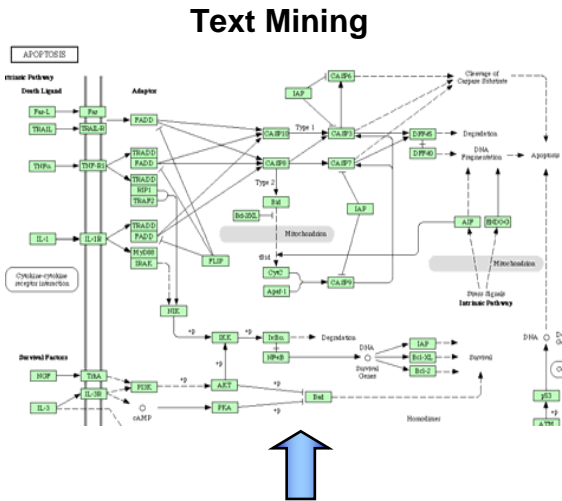


**MITRE**  
Technology  
Program

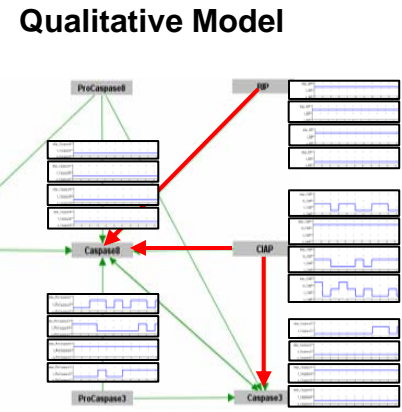
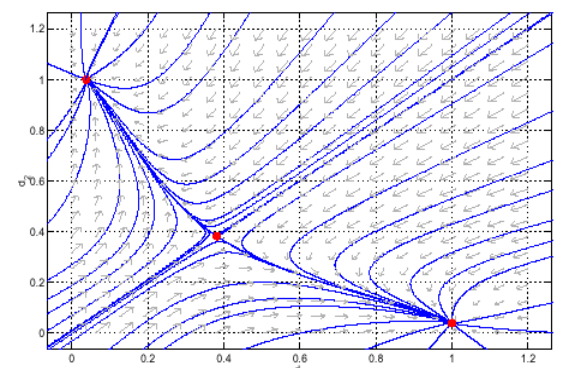
# Problem

- **Growth of biotechnology has been tremendous.**
  - Trajectory similar to 20<sup>th</sup> century electronics industry
- **This growth has lowered barriers to entry for constructing novel biological agents.**
  - A key challenge of the asymmetric threat
- **Modeling and simulation can be used to dramatically improve consequence management.**
  - Elucidate pathogenic mechanisms
  - Development of intervention strategies

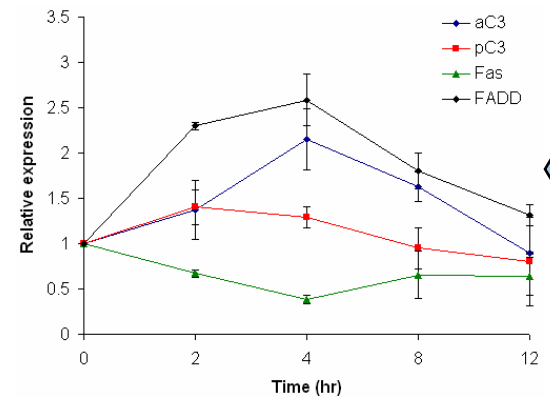
# Background



Model Exploration



Experimental Validation



Quantitative Model

$$\begin{aligned}
 \frac{d[RL]_t}{dt} &= r_t - \mu[RL]_t & \frac{d[c_{2a}]}{dt} &= \Omega_{2a} - 2r_{2a} - \mu[c_{2a}] \\
 \frac{d[R]_t}{dt} &= \Omega_R - \mu[R]_t & \frac{d[c_{2b}]}{dt} &= 2r_{2b} - \mu[c_{2b}] \\
 \frac{d[F]}{dt} &= \Omega_F - 2r_F - \mu[F] & \frac{d[c_{2c}]}{dt} &= \Omega_{2c} - \sum_{i=1}^n r_{c_{2i}} - \mu[c_{2c}] \\
 \frac{d[RL.F_2]_t}{dt} &= r_r - \mu[RL.F_2]_t & \frac{d[c_{2d}]}{dt} &= \sum_{i=1}^n r_{c_{2i}} - \mu[c_{2d}] - r_{c_{2d}} \\
 \frac{d[C_1]}{dt} &= r_c - r_{c1} - \mu[C_1] & \frac{d[b]}{dt} &= \Omega_b - \mu[b] \\
 \frac{d[A]_t}{dt} &= \Omega_{A1} - \mu[A]_t & \frac{d[I_c]}{dt} &= \Omega_{I_c} - \mu[I_c] \\
 \frac{d[A.C_2]}{dt} &= r_{A1} - \mu[A.C_2] & &
 \end{aligned}$$

Parameter Estimation

```

su = array(0.05, 'd');
mu = array(0.05, 'd');

[]
# kaf=2 and kt=2 are original values in code and are 'rate determining'
# steps: update idx to include indices for the new params.
idx = update(idx, [1, 2, 3, 4]);
k = array(10, 1, 2, 1, 10); #states

optimize0.py [Python]-121-- 74
>>> x = [111., 19., 26., 15., 111.]
>>> f = fmin(reaction2, x)
ks(-1): 111.000000    ks1: 19.000000    kt: 26.000000    kal: 15.000000    ka(-1)
ks(-1): 116.550000    ks1: 19.000000    kt: 26.000000    kal: 15.000000    ka(-1)
ks(-1): 111.000000    ks1: 19.950000    kt: 26.000000    kal: 15.000000    ka(-1)
ks(-1): 111.000000    ks1: 19.000000    kt: 27.300000    kal: 15.000000    ka(-1)
ks(-1): 111.000000    ks1: 19.000000    kt: 26.000000    kal: 15.750000    ka(-1)
ks(-1): 111.000000    ks1: 19.000000    kt: 26.000000    kal: 15.000000    ka(-1)
ks(-1): 113.220000    ks1: 19.380000    kt: 26.520000    kal: 15.300000    ka(-1)
:
:
:
ks(-1): 10.000006    ks1: 0.999997    kt: 2.000003    kal: 0.999999    ka(-1)
ks(-1): 9.999877    ks1: 0.999983    kt: 2.000124    kal: 1.000020    ka(-1)
ks(-1): 10.000014    ks1: 1.000002    kt: 1.999977    kal: 0.999996    ka(-1)
ks(-1): 10.000000    ks1: 1.000000    kt: 2.000000    kal: 1.000000    ka(-1)
ks(-1): 10.000036    ks1: 1.000006    kt: 2.000041    kal: 1.000006    ka(-1)
Optimization terminated successfully.
Current function value: 0.000000
Iterations: 602
Function evaluations: 977
    
```

**Iteratively refining computational modeling with experimental techniques**

# Objective

## Utilize computational modeling techniques to speed response to pathogenic agents

- Identify how a biological warfare agent is acting to disrupt normal cellular processes
- Develop and test intervention strategies computationally
- Estimate pathogenicity so countermeasures can be mounted that are commensurate with the posed threat

*Developing computational tools, informatics infrastructure, and interdisciplinary expertise to model cellular systems*

# Activities

- **Construction of qualitative and quantitative models of fas-mediated apoptosis**
  - Programmed cell death pathway that is perturbed by a number of biological warfare agents
- **Participation in experimental studies at the Walter Reed Army Institute of Research**
- **Collaborative efforts with groups in academia**
  - Integration of multiple apoptosis models
- **Development of specifications for wet lab construction**

# Highlight

## Model Reactions

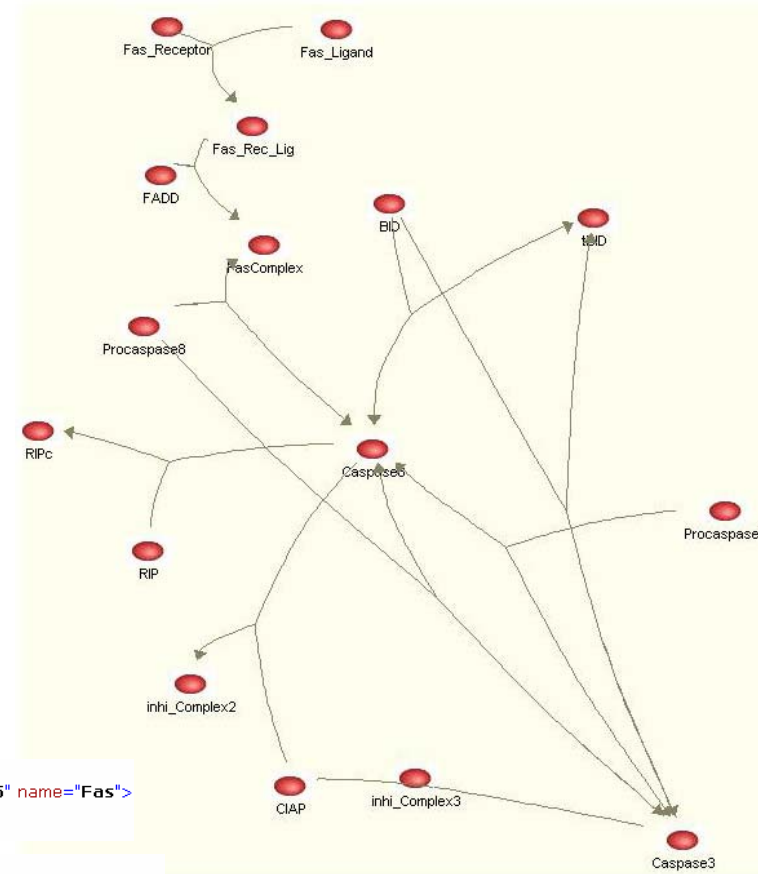
FasR + FasL  $\leftrightarrow$  Fas\_Rec\_Lig  
Fas\_Rec\_Lig + FADD  $\leftrightarrow$  FasComplex  
FasComplex + Procaspase8  $\rightarrow$  Caspase8 + FasComplex  
Caspase8 + BID  $\rightarrow$  tBID + Caspase8  
Caspase3 + BID  $\rightarrow$  tBID + Caspase3  
Caspase8 + RIP  $\rightarrow$  Inhi\_Complex1  
Procaspase8 + Caspase3  $\rightarrow$  Caspase8 + Caspase3  
Caspase8 + Procaspase3  $\rightarrow$  Caspase8 + Caspase3  
Caspase8 + CIAP  $\leftrightarrow$  inhi\_Complex2  
Caspase3 + CIAP  $\leftrightarrow$  inhi\_Complex3  
Caspase8 + RIP  $\rightarrow$  RIPc

## Kinetic law formula

```
- <reaction name="J14" reversible="true">
- <listOfReactants>
  <specieReference specie="Fas" stoichiometry="1" />
</listOfReactants>
- <listOfProducts>
  <specieReference specie="FADD" stoichiometry="1" />
</listOfProducts>
+ <annotations>
- <kineticLaw formula="J14_k1*Fas-J14_k2*FADD">
  - <listOfParameters>
    <parameter name="J14_k1" value="4.6" />
    <parameter name="J14_k2" value="0.1" />
  </listOfParameters>
</kineticLaw>
</reaction>
```

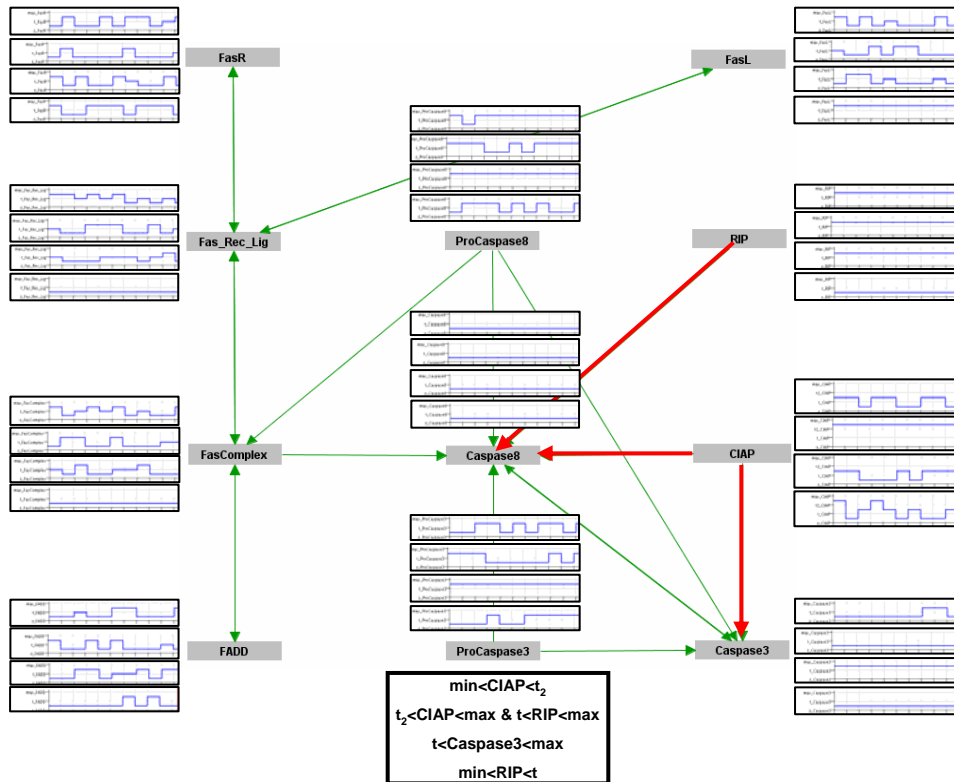
## Protein information

```
</specie>
- <specie boundaryCondition="false" compartment="compartment" initialAmount="65" name="Fas">
+ <annotations>
</specie>
</specie>
- <specie boundaryCondition="false" compartment="compartment" initialAmount="9.6" name="FADD">
+ <annotations>
</specie>
```

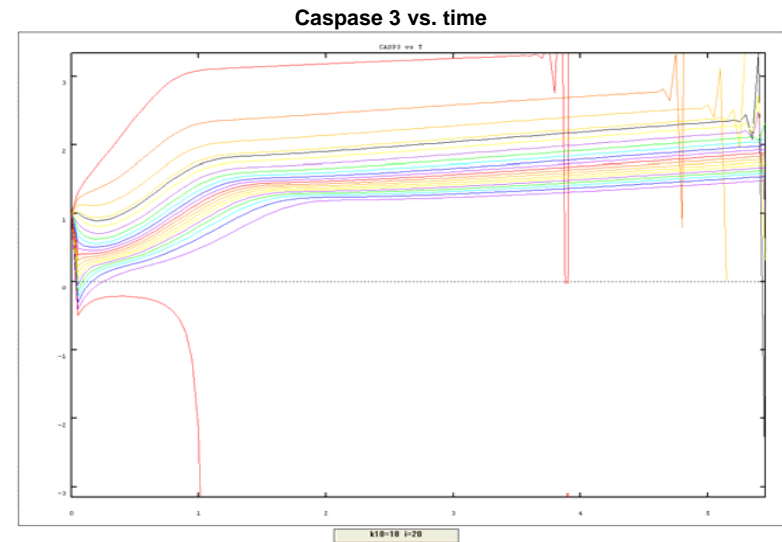


# Demonstration

- Text mining of the literature
- Qualitative simulation
- Creation of network in SBML format
- Quantitative modeling



AGI Explorer - Untitled  
 NCBI PubMed  
 Search PubMed  
 J Biol Chem. 1999 Jun 4;274(23):16337-44  
**The solution structure of FADD death domain interactions of Fas**  
 Jeong EJ, Bang S, Lee TH, Park YI, S  
 Structural Biology Center, Korea Institute of Science and Technology, Seoul, 136-701, Korea.

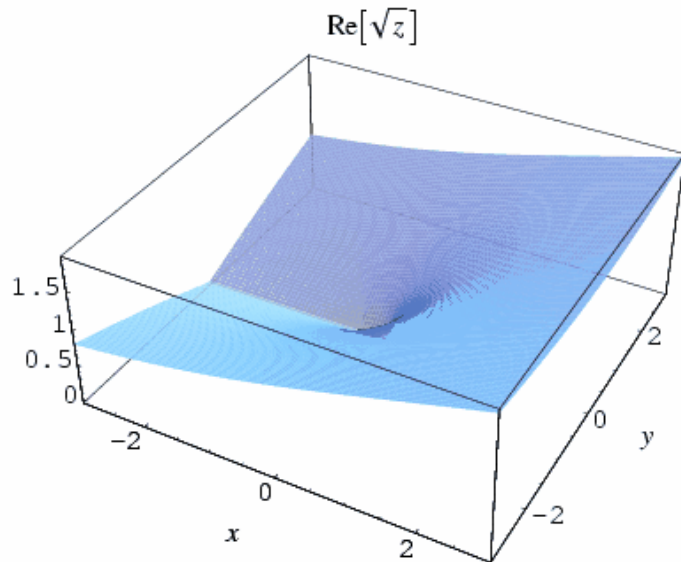


# Impacts

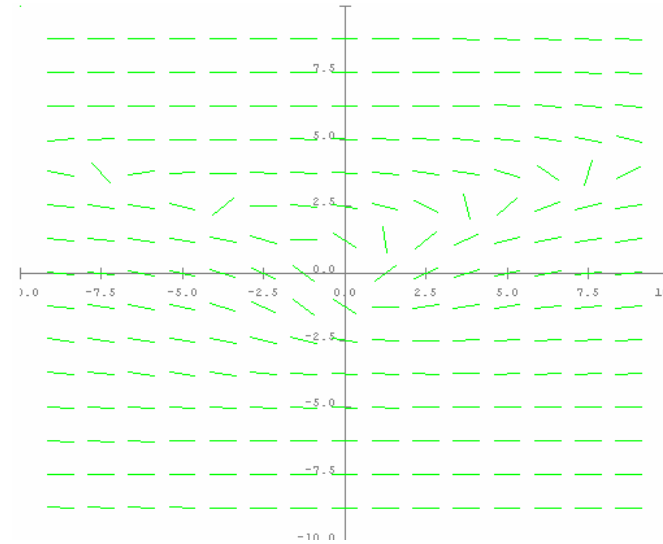
- **Creation of a computational model of apoptosis that is extensible to address implications and therapeutic strategies for other BW agents**
- **Expertise in analysis of BW and CW agents resulted in sponsored work with the US Army Research Institute of Chemical Defense**
- **Development of sponsored work for the Naval Medical Research Center focused on bioinformatics of anthrax**
- **Early collaborative work with the Centers for Disease Control and Prevention resulted in an innovation grant to pursue complementary research**
- **Joined the Institute for Collaborative Biotechnologies**
  - **An Army University Affiliated Research Center (UARC)**
  - **Academic affiliations: UC-Santa Barbara, Caltech, & MIT**

# Future Plans

## Bifurcation Analysis



## Phase-plane Analysis



## • Transcriptional Regulatory Network

