BRIEF SYNOPSIS:

BIOCHEMICAL NETWORKS
- information processing
- decision & control
- effector function

λ PHAGE
- 2 states; long-term stability
- multiple interactions among proteins & binding sites

DIFFERENTIAL EQUATION FORMULATION:

$$\frac{d\vec{x}}{dt} = F(\vec{x},\vec{u}) = A^{(1)}\vec{x} + A^{(2)}(\vec{x}\otimes\vec{x}) + B\vec{u} + \underbrace{C(\vec{u}\otimes\vec{x}) + D(\vec{u}\otimes\vec{u})}_{\text{generally don't write}}$$

For steady states:

$$\frac{d\vec{x}}{dt} = 0 \Rightarrow F(\vec{x},\vec{u}) = 0$$

Solve using NEWTON'S METHOD:

$$\frac{dF(\vec{x},\vec{u})}{d\vec{x}} = \nabla_{\vec{x}} F \equiv J_F(\vec{x})$$

$$F(\vec{x}^1,\vec{u}) = F(\vec{x}^0,\vec{u}) + \underbrace{\frac{dF}{d\vec{x}}(\vec{x}^0,\vec{u})}_{J_F(\vec{x}^0)}(\vec{x}^1 - \vec{x}^0) + \cancel{H.O.T.}$$

Set $F(\vec{x}^1,\vec{u}) = 0 \Rightarrow J_F(\vec{x}^0)(\vec{x}^1 - \vec{x}^0) = -F(\vec{x}^0,\vec{u})$

solve for $\vec{x}^1$

iterate: $J_F(\vec{x}^1)(\vec{x}^2 - \vec{x}^1) = -F(\vec{x}^1,\vec{u})$

$\vdots$

RUN SIMULATIONS:
- Forward Euler – explicit
- Backward Euler – implicit (iterative)

PARAMETER SENSITIVITIES: $\frac{d\vec{x}}{d(\Delta A)}$

of experiments

$$\min_{\Delta A} f(\Delta A) = \min_{\Delta A} \sum_{l=1}^{L} \left[C^T \vec{x}^l(\Delta A) - \overset{[00001000]}{C^T} \vec{x}^{l,\text{measured}}\right]^2$$

OPTIMIZE:

- GRADIENT DESCENT

$$\Delta A' = \Delta A^0 + \beta \nabla_{\Delta A} f$$

pick stepsize β s.t. $\min_{\beta} f(\Delta A^0 + \beta\nabla_{\Delta A} f)$

This method does not work well

- ADJOINT OPTIMIZATION

Set gradient to zero

$$\frac{\partial}{\partial(\Delta A)}\left[C^T\vec{x}^l(\Delta A) - C^T\vec{x}^{l,m}\right]^2$$

$$= 2\underbrace{\left[C^T\vec{x}^l(\Delta A) - C^T\vec{x}^{l,m}\right]}_{\text{straightforward}}\underbrace{\left[\frac{\partial}{\partial(\Delta A)} C^T\vec{x}^l(\Delta A)\right]}_{\text{difficult} \to \text{sensitivities}}$$

$$\frac{\partial}{\partial(\Delta A)} C^T\vec{x}^l(\Delta A) = \underset{1\times n}{C^T}\ \underset{n\times q}{\frac{\partial \vec{x}^l(\Delta A)}{\partial(\Delta A)}}$$

n = # of concentrations
q = # of parameters

$$\underbrace{\frac{dF}{d(\Delta A)} = 0 \Rightarrow \frac{\partial F}{\partial(\Delta A)} + \frac{\partial F}{\partial\vec{x}}\cdot\frac{\partial\vec{x}}{\partial(\Delta A)} = 0}_{(\star)} \Rightarrow \underset{n\times n}{\frac{\partial F}{\partial\vec{x}}}\cdot\underset{n\times q}{\frac{\partial\vec{x}}{\partial(\Delta A)}} = -\underset{n\times q}{\frac{\partial F}{\partial(\Delta A)}}$$

solve for this term & plug-in

HARDER TO SOLVE

Rather than solve the previous problem, SOLVE its DUAL:

$$\frac{\partial}{\partial(\Delta A)} C^T\vec{x}^l(\Delta A) = \underset{1\times n}{z^T}\ \underset{n\times q}{\left(\frac{\partial F}{\partial(\Delta A)}\right)}$$

where z is obtained from:

$$\underset{n\times n}{\left(\frac{\partial F}{\partial\vec{x}}\right)^T}\ \underset{n\times 1}{z} = -\underset{n\times 1}{C}$$

EASIER TO SOLVE

SHOW THAT THE DUAL IS EQUIVALENT:

$$C^T\frac{\partial\vec{x}^l(\Delta A)}{\partial(\Delta A)} = \overbrace{C^T\left(-\frac{\partial F}{\partial\vec{x}}\right)^{-1}}^{z^T}\left(\frac{\partial F}{\partial(\Delta A)}\right)$$

FROM $\star$

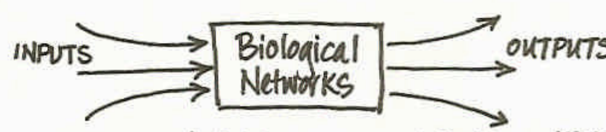
$$\Rightarrow \frac{\partial}{\partial(\Delta A)} C^T\vec{x}^l(\Delta A) = z^T\frac{\partial F}{\partial(\Delta A)}$$

$$z^T = C^T\left(-\frac{\partial F}{\partial\vec{x}}\right)^{-1}$$

$$\Rightarrow z^T\left(\frac{\partial F}{\partial\vec{x}}\right) = -C^T$$

$$\Rightarrow \left(\frac{\partial F}{\partial\vec{x}}\right)^T z = -C \quad \square$$

*Finding Steady States
*Running Simulations
– Model Consruction
- parameter estimation
  - can also be used in design mode
- parameter sensitivities



- absence of glucose
- presence of galactose

- synthesize multiple enzymes for galactose utilization
- turns on galactose transporters

PROBLEMS IN BIOLOGY:
- Difficulty in maintaining constant concentration
  - cell volume changes
  - small counts make uniformity difficult
- Highly variable environment
  - Temperature
  - Humidity
- Certain functions persist across all stages of development, cell cycle, tissue types
- Evolve