Convex design of combination drug therapy

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**Motivation**
- Combination drug therapy
  - Effectively suppresses all mutagens
  - Avoids side effects (from too many drugs)
- Other applications
  - Leader selection in directed networks
  - Design of chemical reaction networks
  - Decentralized control of buildings

**Problem Formulation**

**Evolution model**

\[
\dot{x} = \left( A + \sum_{j=1}^{r} D_{ij} u_{j} \right) x + d
\]

**Linear Dynamics**

- Interpretation
  - \( x_i \) – population of \( i \)th HIV mutagen
  - \( A \) – mutation probabilities and replication rates
  - \( u_{j} \) – dose of \( j \)th drug
  - \( (D_{ij})_{ii} \) – effect of drug \( j \) on mutagen \( i \)
  - \( d \) - disturbances or initial virus populations
- Positive system, i.e., \( x(0) \geq 0 \implies x(t) \geq 0 \)
- Assumptions
  - \( A \) – Metzler matrix (\( A_{ij} \geq 0 \) for all \( i \neq j \))
  - \( D_{ij} \) – diagonal matrices

**Theoretical Contributions**

**Convexity of \( H_2 \) norm wrt \( u \)**
- Energy of the impulse response
  \[
  J_2(u) := \sum_{i} \int_{0}^{\infty} \|x(t)\|_2^2 \, dt, \quad d(t) = e_i \delta(t)
  \]
- Variance amplification of stochastic disturbances
  \[
  J_2(u) = \sum_{i} \lim_{t \to \infty} \text{var}(x_i(t)), \quad d(t) \sim \mathcal{N}(0, I)
  \]

**Convexity of \( H_\infty \) norm wrt \( u \)**
- Induced energy gain; worst-case amplification
  \[
  J_\infty(u) := \sup_{d \neq 0} \int_{0}^{\infty} \|x(t)\|_2 \, dt
  \]

**Combination Drug Therapy Design**

**Convex Optimization Problem**

\[
\text{minimize} \quad J(u) + g(u)
\]

**Objective** – design drug doses to balance

**Performance**:
- \( J(u) \) – \( H_2 \) or \( H_\infty \) norm

**Magnitude/Sparse**:
- \( g(u) \) – Combination of penalties and constraints

**Can impose penalties on**
- size of drug doses \( u^T u \)
- number of drugs \( \gamma \|u\|_1 \)
- (larger \( \gamma \) → less drugs)

**Can impose constraints on**
- Budget \( \sum |u_i| \leq \beta \)
- Maximum dose \( |u_i| \leq \beta_i \)
- Drug \( j \) requiring drug \( i \) \( u_j \leq u_i \)

**Reference**

**HIV Example**

- Sparsity pattern of \( A \)
- 35 HIV mutagens
- 5 broadly neutralizing antibodies

**Budgeted Combination Drug Therapy**
- Budget constraint \( \sum |u_i| \leq 1 \)
- Limited budget also promotes use of fewer drugs

**Aggregate and Worst-Case Response**

The drugged (a) aggregate response, illustrated by the total virus population and the (b) worst case response, here corresponding to the population of mutagen YU2-N280Y-N332K, vs. time. Response is to the initial condition \( x(0) = \frac{1}{\sqrt{35}} \).

**\( H_2 \)- (—) and \( H_\infty \)-Optimal Doses (—) and Performance**

<table>
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<th>Antibody</th>
<th>( u_{H_2} )</th>
<th>( u_{H_\infty} )</th>
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