Convex design of combination drug therapy

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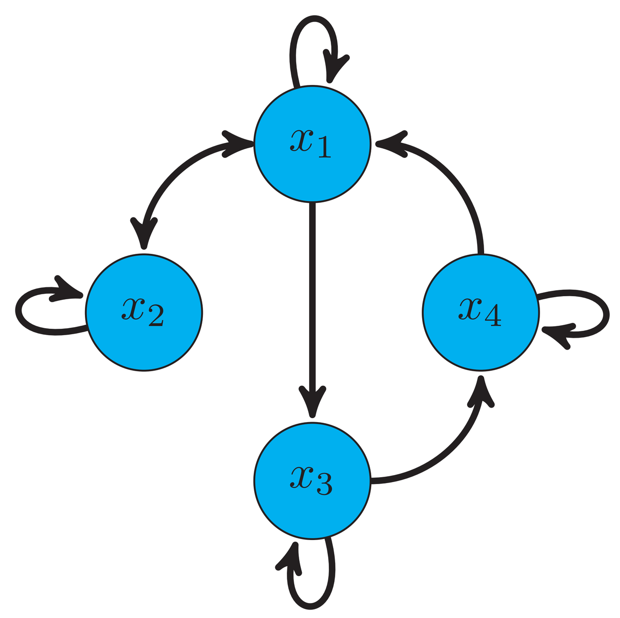
Motivation

- 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



$$\underbrace{\begin{bmatrix} \star & \star & & \star \\ \star & \star & & \\ \star & & \star & \\ & & \star & \star \end{bmatrix}}_{A}$$

Linear Dynamics

$$\dot{x} \;=\; \left(A \,+\, \sum_{j=1}^{r} D_j u_j \right) x \,+\, d$$

- Interpretation
  - x_i – population of ith HIV mutagen
  - A – mutation probabilities and replication rates
  - u_j – dose of jth drug
  - $(D_j)_{ii}$ – 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_j – diagonal matrices

Theoretical contributions

Convexity of $\mathcal{H}_2$ norm wrt u

- Energy of the impulse response

$$J_2(u) \;:=\; \sum_i \int_0^\infty \|x(t)\|_2^2 \, \mathrm{d}t, \qquad d(t) = \mathrm{e}_i \, \delta(t)$$

- Variance amplification of stochastic disturbances

$$J_2(u) \;=\; \sum_i \lim_{t\to\infty} \mathrm{var}\,(x_i(t))\,, \qquad d(t) \sim \mathcal{N}(0, I)$$

Convexity of $\mathcal{H}_\infty$ norm wrt u

- Induced energy gain; worst-case amplification

$$J_\infty(u) \;:=\; \sup_{d \neq 0} \frac{\int_0^\infty \|x(t)\|_2 \, \mathrm{d}t}{\int_0^\infty \|d(t)\|_2 \, \mathrm{d}t}$$

Combination drug therapy design

Convex optimization problem

$$\text{minimize} \;\; J(u) \,+\, g(u)$$

Objective – design **drug doses** to balance

PERFORMANCE: **size of virus population**

- $J(u)$ – $\mathcal{H}_2$ or $\mathcal{H}_\infty$ norm

MAGNITUDE/SPARSITY: **dose size, number of drugs**

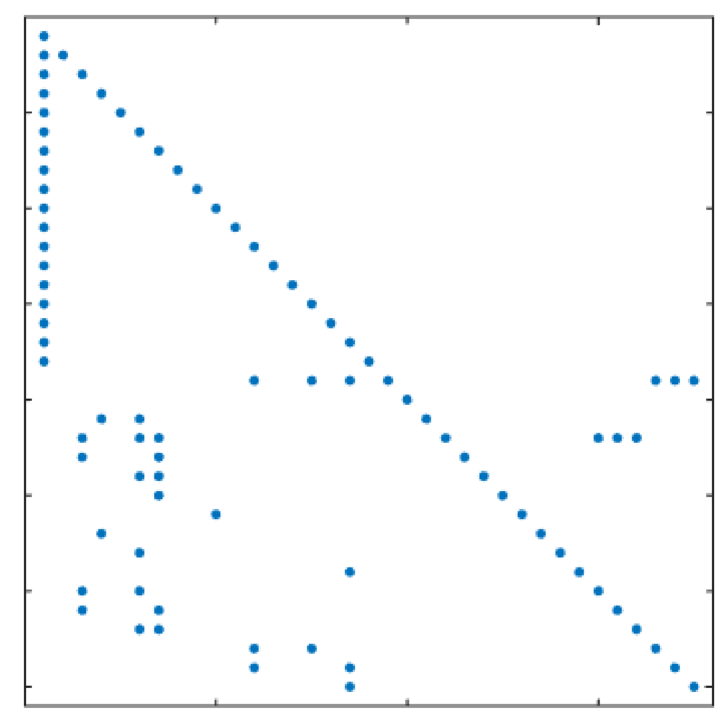
- $g(u)$ – Combination of penalties and constraints
- Can impose penalties on
  - size of drug doses $\quad u^T u$
  - number of drugs $\quad \gamma \|u\|_1$

    (larger $\gamma \to$ less drugs)
- Can impose constraints on
  - Budget $\quad \sum |u_i| \;\leq\; \beta$
  - Maximum dose $\quad |u_i| \;\leq\; \beta_i$
  - Drug j requiring drug i $\quad u_j \;\leq\; u_i$

Reference

N. K. Dhingra, M. Colombino, and M. R. Jovanović, *"On the convexity of a class of structured optimal control problems for positive systems,"* European Control Conference '16 (submitted).

HIV example



– Sparsity pattern of A

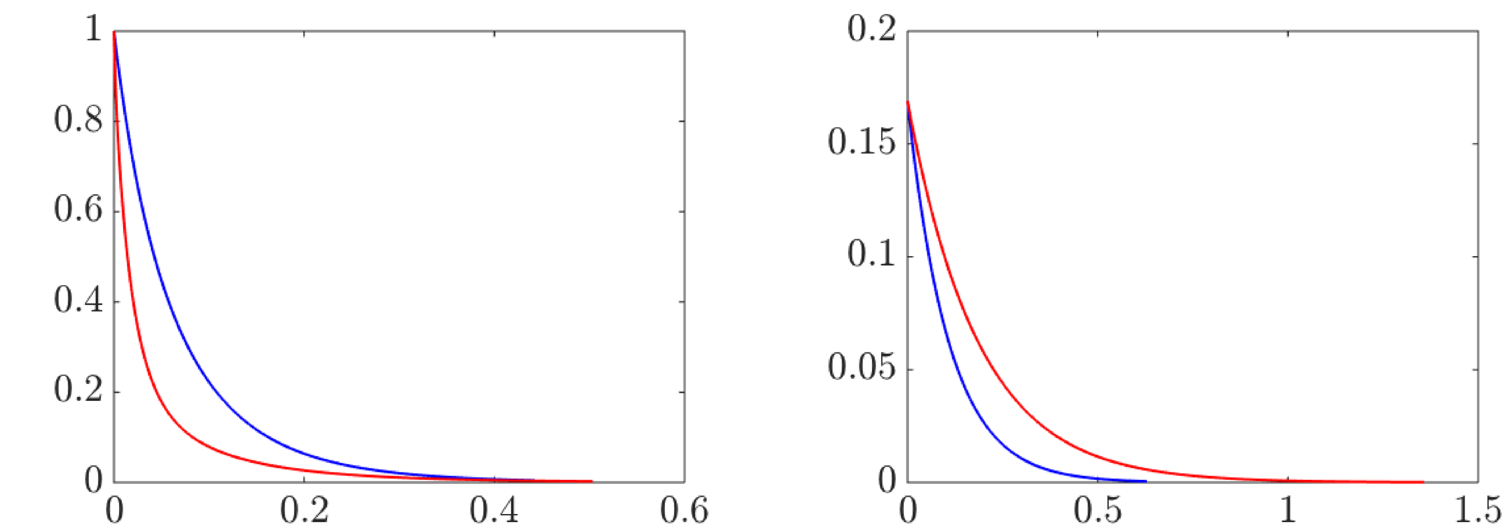
– 35 HIV mutagens

– 5 broadly neutralizing antibodies

Budgeted combination drug therapy

- Budget constraint $\quad \sum |u_i| \;\leq\; 1$
- Limited budget also promotes use of fewer drugs

Aggregate and worst-case response



(a) (b)

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 $x(0) = \frac{1}{\sqrt{35}}\mathbb{1}$.

$\mathcal{H}_2$- (—) and $\mathcal{H}_\infty$-optimal doses (—) and performance

Antibody	$u_{\mathcal{H}_2}$	$u_{\mathcal{H}_\infty}$
3BC176	0.5952	0.9875
PG16	0	0
45-46G54W	0.2484	0.0125
PGT128	0.1564	0.0000
10-1074	0	0

$J_2(u_{\mathcal{H}_2})$	0.6017
$J_2(u_{\mathcal{H}_\infty})$	1.1947
$J_\infty(u_{\mathcal{H}_2})$	0.1857
$J_\infty(u_{\mathcal{H}_\infty})$	0.1084

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