

## Outline

## **Integral Quadratic Constraint**

- Positive Definite Decomposition
- Scalable IQC analysis
- Positive and Monotone Systems
- Concluding remarks

$$\xrightarrow{v}$$
  $\Delta$ 

The (possibly nonlinear) operator  $\Delta$  on  $\mathbf{L}_2^m[0,\infty)$  is said to satisfy the IQC defined by  $\Pi$  if

$$\int_{-\infty}^{\infty} \left[ \begin{array}{c} \widehat{v}(i\omega) \\ \widehat{(\Delta v)}(i\omega) \end{array} \right]^* \Pi(i\omega) \left[ \begin{array}{c} \widehat{v}(i\omega) \\ \widehat{(\Delta v)}(i\omega) \end{array} \right] d\omega \ge 0$$

for all  $v \in \mathbf{L}_2[0,\infty)$ .







A describes the mutation dynamics without drugs, while  $D^1, \ldots, D^m$  are diagonal matrices modeling drug effects.

Determine  $u_1, \ldots, u_m \ge 0$  with  $u_1 + \cdots + u_m \le 1$  such that x decays as fast as possible!

[Jonsson, Rantzer, Murray, ACC 2014]

or equivalently

 $\frac{A_k\xi}{\xi_k} - \sum_i u_i D_k^i + \gamma < 0$ 

Maximizing  $\gamma$  is convex optimization in  $(\log \xi_i, u_i, \gamma)$  !

## **Using Measurements of Virus Concentrations**

 $\dot{x}(t) = \left(A - \sum_{i} u_i(t)D^i\right)x(t)$ 

Can we get faster decay using time-varying u(t) based on

Evolutionary dynamics:

measurements of x(t) ?

### **Convex Monotone Systems**

The system

$$f(x(t), u(t)), x(0) = a$$

is a monotone system if its linearization is a positive system. It is a convex monotone system if every row of f is also convex.

Theorem. [Rantzer/ Bernhardsson (2014)]

 $\dot{x}(t$ 

For a convex monotone system  $\dot{x} = f(x, u)$ , each component of the trajectory  $\phi_t(a, u)$  is a convex function of (a, u).

# **Using Measurements of Virus Concentrations**

The evolutionary dynamics can be written as a convex monotone system:

$$rac{d}{dt}\log x_k(t) = rac{A_k x(t)}{x_k(t)} - \sum_i u_i(t) D_k^i$$

Hence the decay of  $\log x_k$  is a convex function of the input and optimal trajectories can be found even for large systems.

## Example



# $A = \begin{bmatrix} -\delta & \mu & \mu & 0\\ \mu & -\delta & 0 & \mu\\ \mu & 0 & -\delta & \mu\\ 0 & \mu & \mu & -\delta \end{bmatrix}$

clearance rate  $\delta = 0.24 \text{ day}^{-1}$ , mutation rate  $\mu = 10^{-4} \text{ day}^{-1}$ and replication rates for viral variants and therapies as follows

Variant	Therapy 1	Therapy 2	Therapy 3
Wild type $(x_1)$	$D_1^1 = 0.05$	$D_1^2 = 0.10$	$D_1^3 = 0.30$
Genotype 1 $(x_2)$	$D_2^{\bar{1}} = 0.25$	$D_2^{ar{2}} = 0.05$	$D_2^{\bar{3}} = 0.30$
Genotype 2 $(x_3)$	$D_3^{\tilde{1}} = 0.10$	$D_3^{\overline{2}} = 0.30$	$D_3^{\overline{3}} = 0.30$
HR type $(x_4)$	$D_4^{1} = 0.30$	$D_4^2 = 0.30$	$D_4^3 = 0.15$

## Summary



IQC analysis scales using positive definite decompositions !

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Scalability comes from monotonicity.

### **Example**