Controllability Metrics in Markov Decision Linear Models of Gene Networks

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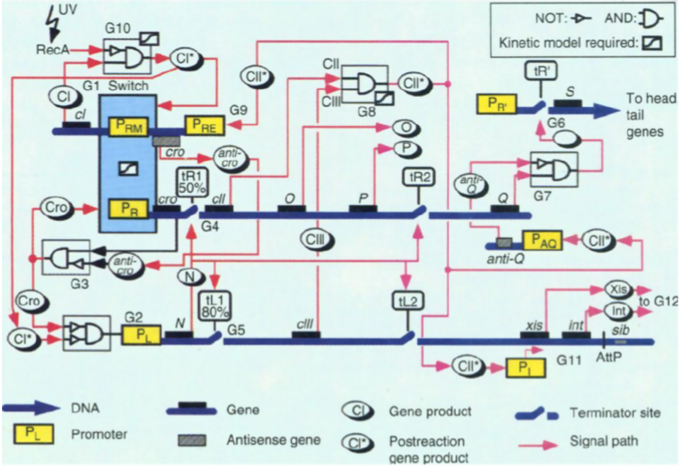
Outline

1. The model
   - Biochemical Reactions
   - Mathematical Model
   - The Questions
2. Controllabilities
   - Metric By Observability
   - Riccati Formulation of the Metric
   - Main Theoretical Results
3. Minimal Intervention
   - Optimization Problems
   - Back to Lambda

Lambda Phage



from McAdams and Shapiro, Science 1995

Reference Model

- Biochemical reactions

$$2R_1 \overset{K_1}{\rightleftarrows} R_2,\ D\left(+R_2\right) \overset{K_2}{\rightleftarrows} DR_2,\ D\left(+R_2\right) \overset{K_3}{\rightleftarrows} DR_2^*,$$
$$DR_2\left(+R_2\right) \overset{K_4}{\rightleftarrows} DR_2R_2,\ DR_2 + P \overset{K_t}{\rightarrow} DR_2 + P + rR_1,\ R_1 \overset{K_d}{\rightarrow} .$$

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- Groups of reaction

trend : DNA mechanism of the host E-Coli $(D, DR_2, DR_2^*, DR_2R_2)^T$

update : $2R_1 \overset{K_1}{\rightleftarrows} R_2,\ R_1 \overset{K_d}{\rightarrow}$

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rare : $DR_2 + P \ \overset{K_t}{\to} DR_2 + P + rR_1$
- Some mathematical models $(d_1, d_2, d_3, d_4, x_1, x_2)$:
pure jump, 2-scale PDMP, Marked-point, discrete model
Reaction speeds can be "chosen".

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- In general, since only one type of occupation, one gets basis vectors e_1 (D), e_2 (DR_2) ... e_p
- Take $\Delta M_{n+1} = L_{n+1} -$ "*average*" (in fact $\mathbb{E}\left[L_{n+1}/\mathcal{F}_n\right]$)
  To make it simple, assume L_{n+1} is completely independent of L_n and has $0-$mean
  $\Delta M_{n+1} = L_{n+1}$

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- linearized
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- or, again $dX_s^{x,u} = [A(\gamma_s)\,X_s^{x,u} + B_s u_s]\,ds$
- discrete $X_{n+1}^{x,u} = A_n(\omega)\,X_n^{x,u} + Bu_{n+1}$

Rare (and Synthesis)

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- Continuous f (config. DNA γ, reaction speeds u, fast variable X)
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- The "expected" behavior is similar ... (is it ?)

The Questions

- For the reference model, one has bistability
  E.g. lytic : for some choice of speeds, lysis occurs (say at time T or N) i.e. $X_T = 0$ (or, more general $X_T =$target).
- from arbitrary x to "almost" 0
- from arbitrary x exactly to 0
- from arbitrary x exactly/almost to any "possible" target

Outline

A Hint to the Metric

- In deterministic update $X_{n+1}^{x,u} = AX_n^{x,u} + Bu_{n+1}$.
- "the dual" $Y_N = y$, $Y_n^{N,y} := A^T Y_{n+1}^{N,y}$
$$\langle X_N, Y_N \rangle = \left\langle x, Y_0^{N,y} \right\rangle + \sum_{n=0}^{N-1} \left[\left\langle u_{n+1}, B^T Y_{n+1}^{N,y} \right\rangle \right].$$
- In order for $X_N^{x,u} = 0$, whenever all $B^T Y_{n+1}^{N,\xi} = 0$, should have $Y_0^{N,y} = 0$
- If "reversible" dynamics, $Y_{n+1} = \left(A^T\right)^{-1} Y_n$
$B^T \left(A^T\right)^{-k} y_0 = 0$ for all $k \leq N$ should imply $y_0 = 0$.
- controllability to 0 iff metric $\left(\cdot^2\right)$
$y \mapsto y^T \left[\sum_{k=1}^N A^{-k} BB^T \left(A^T\right)^{-k}\right] y$
- (in continuous case, application to power electronic actuator placement Summers, Cortesi, Lygeros '14)

Towards Riccati-like Formulation

- Recall that
  $X_{n+1}^{x,u} = A_n(\omega) X_n^{x,u} + Bu_{n+1} + \sum_{i=1}^{p} \langle \Delta M_{n+1}, e_i \rangle C_{i,n}(\omega) X_n^{x,u}$
- Let us look at $\sum_{k=1}^{N} A^{-k} BB^T \left(A^T\right)^{-k}$
  Recursively computed as $P_N = BB^T$,
  $P_n = A^{-1}\left(p_{n+1} + BB^T\right)\left(A^T\right)^{-1}$
- How to deal with non-homogeneity (dependence on n) ?
  Well ... $P_n = A_n^{-1}\left(P_{n+1} + BB^T\right)\left(A_n^T\right)^{-1}$
- How to deal with with stochasticity ?
  Problem : too much information in p_{n+1} which is not available at time n
  Solution : decompose P_{n+1} in what is known at time n and some random variation
  Couple (p, q) .

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- One "corrects" by substracting "horrible terms" $-\alpha_n^T \eta_n^{-1} \alpha_n$
  $\alpha_n := -q_n \times bruit^2 \times \left[A_n^T \right]^{-1}$
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- Problem η_n is only semi-positive definite.
- Solution : penalize by adding εI

Horrible Terms (you may look away for 2 minutes)

- In fact, $P^{\varepsilon}_{n+1} = \underbrace{\mathbb{E}\left[P^{\varepsilon}_{n+1}/\mathcal{F}_n\right]}_{p} + \underbrace{Q^{\varepsilon}_{n} diag\left(\Delta M_{n+1}\right)}_{q}$,
- $P^{\varepsilon}_{n} = A_n^{-1}\left(\mathbb{E}\left[P^{\varepsilon}_{n+1}/\mathcal{F}_n\right] + BB^T\right)\left[A_n^T\right]^{-1} - \alpha^T_{n,\varepsilon}\eta^{-1}_{n,\varepsilon}\alpha_{n,\varepsilon}$,
- $\alpha^j_{n,\varepsilon} := -Q^{\varepsilon}_n\mathbb{E}\left[\left\langle \Delta M_{n+1}, e_j\right\rangle diag\left(\Delta M_{n+1}\right)/\mathcal{F}_n\right]\left[A_n^T\right]^{-1}$
- $\eta^{j,k}_{n,\varepsilon} :=$
  $\varepsilon\delta_{j,k}I_{m\times m} + \frac{1}{2}Q^{\varepsilon}_n\mathbb{E}\left[\left\langle \Delta M_{n+1}, e_k\right\rangle\left\langle \Delta M_{n+1}, e_j\right\rangle diag\left(\Delta M_{n+1}\right)/\mathcal{F}_n\right]$
  $+\frac{1}{2}\mathbb{E}\left[\left\langle \Delta M_{n+1}, e_k\right\rangle\left\langle \Delta M_{n+1}, e_j\right\rangle\left(diag\left(\Delta M_{n+1}\right)\right)^T/\mathcal{F}_n\right]\left(Q^{\varepsilon}_n\right)^T$
  $+\mathbb{E}\left[\left\langle \Delta M_{n+1}, e_k\right\rangle\left\langle \Delta M_{n+1}, e_j\right\rangle/\mathcal{F}_n\right]\mathbb{E}\left[P^{\varepsilon}_{n+1}/\mathcal{F}_n\right]$
- If C is present, even more "horrible terms" α, η.
- JUST A,B condition does not suffice ®

Theorem

i. System is controllable to 0 $\Leftrightarrow$ *almost to* $0 \Leftrightarrow \liminf_{\varepsilon \to 0+} P_0^\varepsilon \gg 0$ *(positive definite).*

ii. The norm is $\|y_0\|_{ctrl}^2 = \liminf_{\varepsilon \to 0} \left\langle P_0^\varepsilon y_0, y_0 \right\rangle.$

Existence results :

iii. If A_n, C_n *are non-random,* $\exists P^\varepsilon \geq 0$ *(explicit).*

iv. If $C_n = 0$, $\exists P^\varepsilon \geq 0$ *(explicit).*

v. continuous and discrete conditions are NOT the same.

Outline

Scenarios, Efficiency

- Several (r) scenarios $(B_i)_{i\in\{1,..,r\}}$: $\|\cdot\|_{ctrl,\boxed{\text{B}}}$
- $\|B\|_{ctrl}^{spec} := \inf_{y\neq 0} \frac{\|y\|_{ctrl,B}}{\|y\|}$

  $\|B\|_{ctrl}^{rank} := Rank\left(\liminf_{\varepsilon\to 0} P_0^{\varepsilon}(B)\right)$
- controllable using $B \Leftrightarrow \|B\|_{ctrl}^{spec} > 0 \Leftrightarrow \|B\|_{ctrl}^{rank} = m.$

Definitions

1)$\mathcal{I}$ is minimal spectral-efficient intervention :
(i) $\|B(\mathcal{I})\|_{ctrl}^{spec} > 0$;
(ii) $\forall \mathcal{J} \subset \{1,...r\}$, $|\mathcal{J}| < |\mathcal{I}|$, one has $\|B(\mathcal{J})\|_{ctrl}^{spec} = 0$;
(iii) $\forall \mathcal{J} \subset \{1,...r\}$, $|\mathcal{J}| = |\mathcal{I}|$, one has $\|B(\mathcal{J})\|_{ctrl}^{spec} \leq \|B(\mathcal{I})\|_{ctrl}^{spec}$.
2) $\mathcal{I}$ is minimal rank-efficient intervention :
(i) $\|B(\mathcal{I})\|_{ctrl}^{rank} = m$;
(ii) $\forall \mathcal{J} \subset \{1,...r\}$, $|\mathcal{J}| < |\mathcal{I}|$, one has $\|B(\mathcal{J})\|_{ctrl}^{rank} < m$.

Optimization Problems

- $\max_{\substack{\mathcal{I}\subset\{1,\ldots r\} \\ |\mathcal{I}|=k}} \|B(\mathcal{I})\|_{ctrl}$, $1 \leq k \leq r$,
- rank-based set functions are submodular (Lovasz '83) :
  $f(S_1 \cap S_2) + f(S_1 \cup S_2) \leq f(S_1) + f(S_2)$
- submodularity is "a combinatorial analogue of concavity" (Nemhauser '78)
  problem is NP-hard BUT a greedy approach provides good results.
- SO : use $\|\cdot\|_{ctrl}^{rank}$ and greedy heuristic $\Rightarrow$ minimal k
  then, use $\|\cdot\|_{ctrl}^{spec}$ for such k.

Back to the Initial Model

- $X_{n+1}^{x,u} = A_n(\omega) X_n^{x,u} + Bu_{n+1} + \sum_{i=1}^{p} \langle \Delta M_{n+1}, e_i \rangle C_{i,n}(\omega) X_n^{x,u}$
- $A = \begin{pmatrix} \frac{1}{4} & \frac{1}{2} \\ \frac{1}{4} & \frac{3}{4} \end{pmatrix}$, $C_2 = \begin{pmatrix} 0 & r \\ 0 & 0 \end{pmatrix}$
- $b_1 = \begin{pmatrix} 0 \\ 1 \end{pmatrix}$, respectively $b_2 = \begin{pmatrix} 1 \\ 1 \end{pmatrix}$
- direct control on dimer fails to work
- one needs SIMULTANEOUS control on monomer/dimer BUT altering ONE external factor suffices.

Thank you for your patience !