1 Convex sets (2 points)

The point of problems in this section is to get you familiar with the concept of convexity.

1.1 Definition of convexity

Choose a problem from below.

1. (Exercise 2.1 of [1].) Let $C \subseteq \mathbf{R}^n$ be a convex set, with $x_1, \ldots, x_k \in C$, and let $\theta_1, \ldots, \theta_k \in \mathbf{R}$ satisfy $\theta_i \geq 0$, $\theta_1 + \cdots + \theta_k = 1$. Show that $\theta_1 x_1 + \cdots + \theta_k x_k \in C$. (The definition of convexity is that this holds for $k = 2$; you must show it for arbitrary k.) Hint: Use induction on k.

2. (Exercise 2.2 of [1].) Show that a set is convex if and only if its intersection with any line is convex. Show that a set is affine if and only if its intersection with any line is affine.

3. (Exercise 2.3 of [1].) *Midpoint convexity.* A set C is *midpoint convex* if whenever two points a, b are in C, the average or midpoint $\frac{a+b}{2}$ is in C. Obviously a convex set is midpoint convex. It can be proved that under mild conditions, midpoint convexity implies convexity. As a simple case, prove that if C is closed and midpoint convex, then C is convex.

4. (Exercise 2.4 of [1].) Show that the convex hull of a set S is the intersection of all convex sets that contain S. (The same method can be used to show that the conic, or affine, or linear hull of a set S is the intersection of all conic sets, or affine sets, or subspaces that contain S.)

Solution : *You can use this solution environment to help organize your answers.*

1.2 Polyhedra

1. Show that a polyhedron $\{x \in \mathbf{R}^n : Ax \preceq b\}$ for some $A \in \mathbf{R}^{m \times n}$ and $b \in \mathbf{R}^m$, is convex. Recall that $\preceq$ means element-wise less than or equal, which is the same as the ordering induced by the proper cone that is the positive orthant $\mathbf{R}^n_+$.

2. (Exercise 2.8 of [1].) Which of the following sets S are polyhedra? If possible, express S in the form $S = \{x | Ax \preceq b, Fx = g\}$. Show solution for at least one of the following sets.

   (a) $S = \{y_1 a_1 + y_2 a_2 \mid -1 \leq y_1 \leq 1, -1 \leq y_2 \leq 1\}$, where $a_1, a_2 \in \mathbf{R}^n$.

   (b) $S = \{x \in \mathbf{R}^n \mid x \succeq 0, \mathbf{1}^\intercal x = 1, \sum_{i=1}^n x_i a_i = b_1, \sum_{i=1}^n x_i a_i^2 = b_2\}$, where $a_1, \ldots, a_n \in \mathbf{R}$ and $b_2, b_2 \in \mathbf{R}$.

   (c) $S = \{x \in \mathbf{R}^n \mid x \succeq 0, x^\intercal y \leq 1 \text{ for all } y \text{ with } \|y\|_2 = 1\}$.

   (d) $S = \{x \in \mathbf{R}^n \mid x \succeq 0, x^\intercal y \leq 1 \text{ for all } y \text{ with } \sum_{i=1}^n |y_i| = 1\}$.

1.3 Quadratic inequality

(Exercise 2.10 of [1].) Let $C \subseteq \mathbf{R}^n$ be the solution set of a quadratic inequality,

$$C = \{x \in \mathbf{R}^n \mid x^\intercal Ax + b^\intercal x + c \leq 0\},$$

with $A \in \mathbf{S}^n$, $b \in \mathbf{R}^n$, and $c \in \mathbf{R}$.

(a) Show that C is convex if $A \succeq 0$.

(b) Show that the intersection of C and the hyperplane defined by $g^\intercal x + h = 0$ (where $g \neq 0$) is convex if $A + \lambda gg^\intercal \succeq 0$ for some $\lambda \in \mathbf{R}$.

1.4 Positive semidefinite cone

Give an explicit description of the positive semidefinite cone $\mathbf{S}_+^n$ in terms of the matrix coefficients and ordinary inequalities, for $n = 1, 2, 3$. To describe a general element of $\mathbf{S}^n$, use the notation

$$x_1, \quad \begin{bmatrix} x_1 & x_2 \\ x_2 & x_3 \end{bmatrix}, \quad \begin{bmatrix} x_1 & x_2 & x_3 \\ x_2 & x_4 & x_5 \\ x_3 & x_5 & x_6 \end{bmatrix}.$$

2 Separating hyperplane (1 point)

Strictly positive solution of linear equations. (Exercise 2.20 of [1].) We discussed the proof of the separating hyperplane theorem and how it can be applied to obtain the theorem of alternative for strict linear inequalities. These topics are also discussed in detail in Section 2.5.1 of the textbook [1]. In this exercise, we apply the same technique for strictly positive solutions of linear equations.

Suppose $A \in \mathbf{R}^{m\times n}$, $b \in \mathbf{R}^m$, and b is in $\mathcal{R}(A) = \{Ax : x \in \mathbf{R}^n\}$, the range of A. Show that there exists an x satisfying

$$x \succ 0, \quad Ax = b$$

if and only if there exists no $\lambda \in \mathbf{R}^m$ with

$$A^\intercal\lambda \geq 0, A^\intercal\lambda \neq 0, \qquad b^\intercal\lambda \leq 0.$$

We will work out the proof in the following steps.

1. Since we have equality $Ax = b$, we would like to know better about this solution space. Recall from linear algebra, that since b is in the range of A, at least one nonzero solution exists, and we denote it x_0. Let the rank of A be r. If $r = n$, then the solution $x = x_0$ is unique, and can be found by taking a right-inverse of A since A has full column rank. Such inverse is often denoted as the pseudoinverse $A^\dagger$ of A, satisfying $AA^\dagger = \mathbf{I}$. Explicitly write down the matrix $A^\dagger$ in this case in terms of A, $A^\intercal$ and inverses. Show that the unique solution is $x_0 = A^\dagger b$.

2. If $r < n$, this means there are infinitely many solutions, and these solutions form a subspace of dimension $n - r$. This space of solutions can be expressed as $x_0 + v$, where x_0 is one particular solution, and v is any vector in $\mathcal{N}(A) = \{v : Av = 0\}$, the null space of A. Check that any such $x_0 + v$ is a solution.

3. Now, let us show the following fact from linear algebra: $c^\intercal x = d$ for all x satisfying $Ax = b$ if and only if there is a vector λ such that $c = A^\intercal\lambda$, $d = b^\intercal\lambda$.

   Hint: Use the rank-nullity theorem. Generically, the nullspace $\mathcal{N}(A)$ of A is a dimension $n - r$ subspace of $\mathbf{R}^n$, and the range of $A^\intercal$ is a dimension r subspace of $\mathbf{R}^n$, and these two spaces are orthogonal complements of each other, i.e. $\mathcal{R}(A^\intercal) \oplus \mathcal{N}(A) = \{u + v : u \in \mathcal{R}(A^\intercal), v \in \mathcal{N}(A)\} = \mathbf{R}^n$. In other words, if a vector u is orthogonal to $\mathcal{N}(A)$, then it is in $\mathcal{R}(A^\intercal)$, and conversely, if a vector is orthogonal to $\mathcal{R}(A^\intercal$, then it is in $\mathcal{N}(A)$. You can show that $c^\intercal v + c^\intercal x_0 = d$ for all $v \in \mathcal{N}(A)$, which implies $c^\intercal v = 0$, so c is orthogonal to $\mathcal{N}(A)$, meaning $c \in \mathcal{R}(A^\intercal)$.

4. Now we have all the tools we need. To prove our result about strictly positive solutions of linear equations, we use a standard separating hyperplane argument. Consider $C = \mathbf{R}_{++}^n$ and $D = \{x \mid Ax = b\}$. Show that C and D are disjoint if and only if there exists $c \neq 0$ and d such that $c^\intercal x \geq d$ for all $x \in C$, and $c^\intercal x \leq d$ for all $x \in D$.

5. Show that the condition on C means $c \succeq 0$ and $d \leq 0$. Also show that $c^\intercal x \leq d$ on D means $c^\intercal x$ is a constant. We can relabel d such that it is this constant and we obtain $c^\intercal x = d$ on D. (Hint: D is an affine set, so contains lines.)

6. Use our conclusion from part 3 to show the full result.

3 Perspective and epigraph (2 points)

3.1 Perspective function

The perspective function is defined by $P : \mathbf{R}^{n+1} \to \mathbf{R}^n$, with domain $\mathbf{R}^n \times \mathbf{R}_{++}$, with $P(z,t) = \frac{z}{t}$. Intuitively, the perspective function is a mapping of images through a pin-hole camera, so it maps a convex set to a convex set, and vice versa. This problem guides you through the proof of this statement.

1. Show that the perspective function maps a line segment to a line segment. (Hint: consider two points, $x = (\tilde{x}, x_{n+1})$ and $y = (\tilde{y}, y_{n+1})$ in $\mathbf{R}^{n+1}$, with $x_{n+1}, y_{n+1} > 0$, then the line segment between them is $\{\theta x + (1-\theta) y : \theta \in [0,1]\}$. Calculate $P(\theta x + (1-\theta)y)$ and write it as the convex combination of $P(x)$ and $P(y)$.)

2. Show that if C is convex, then $P(C)$ is convex, by showing that any line segment in C is also mapped to a line segment in $P(C)$.

3. Show that if C is convex, then $P^{-1}(C)$ is also convex.

4. *Image of polyhedral sets under the perspective function.* (Exercise 2.17 of [1].) For at least one of the following sets C, give a simple description of $P(C)$.

   (a) The polyhedron $C = \mathrm{conv}\{(v_1, t_1), \ldots, (v_k, t_k)\}$ where $v_i \in \mathbf{R}^n$ and $t_i > 0$.

   (b) The hyperplane $C = \{(v,t) \mid f^\intercal v + gt = h\}$ (with f and g not both zero).

   (c) The halfspace $C = \{(v,t) \mid f^\intercal v + gt \leq h\}$ (with f and g not both zero).

   (d) The polyhedron $C = \{(v,t) \mid Fv + gt \preceq h\}$.

3.2 Epigraph

Recall that the graph of a function $f : \mathbf{R}^n \to \mathbf{R}$ is $\{(x, f(x)) \mid x \in \mathbf{dom}\, f\}$, a subset of $\mathbf{R}^{n+1}$. The *epigraph* of $f : \mathbf{R}^n \to \mathbf{R}$ is $\mathbf{epi}\, f = \{(x,t) \mid x \in \mathbf{dom}\, f, f(x) \leq t\}$. (Epi means above.) And f is a convex function if and only if $\mathbf{epi}\, f$ is a convex set.

Use Epigraph to prove the *matrix fractional function*, $f : \mathbf{R}^n \times \mathbf{S}^n \to \mathbf{R}$, $f(x,Y) = x^\intercal Y^{-1} x$, is convex on $\mathbf{dom}\, f = \mathbf{R}^n \times \S^n_{++}$. This is a generalization of the quadratic-over-linear function $f(x,y) = x^2/y$, $\mathbf{dom}\, f = \mathbf{R} \times \mathbf{R}_{++}$.

1. The tool of Schur complement. Consider a block matrix

$$X = \begin{bmatrix} A & B \\ B^\intercal & C \end{bmatrix}$$

   where A and C are symmetric and $C \succ 0$, then the Schur complement of C in X is $S = A - BC^{-1}B^\intercal$.

   Consider the quadratic function

$$g(x,y) = x^\intercal A x + 2x^\intercal B y + y^\intercal C y = \begin{bmatrix} x \\ y \end{bmatrix}^\intercal \begin{bmatrix} A & B \\ B^\intercal & C \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix}.$$

Assume this function is convex in x, y, i.e. $X \succeq 0$. Then consider the function $h(x) = \inf_y f(x, y)$. Show that it is $h(x) = x^\intercal(A - BC^{-1}B^\intercal)x = x^\intercal Sx$.

Then conclude by the minimization rule of convex functions that $S \succeq 0$. In other words, given $C \succ 0$, $X \succeq 0$ if and only if $S \succeq 0$.

2. Show that the epigraph of f can be written as

$$\textbf{epi}\, f = \left\{ (x, Y, t) \,\middle|\, \begin{bmatrix} Y & x \\ x^\intercal & t \end{bmatrix} \succeq 0, Y \succ 0 \right\},$$

using the Schur complement condition for positive semidefiniteness of a block matrix. Then conclude that $\textbf{epi}\, f$ is convex in (x, Y, t). (Hint: Linear matrix inequality.)

3. *First order condition of convex functions and supporting hyperplane for epigraphs.* Given f is convex, show that if $(y, t) \in \textbf{epi}\, f$ then

$$\begin{bmatrix} \nabla f(x) \\ -1 \end{bmatrix}^\intercal \left(\begin{bmatrix} y \\ t \end{bmatrix} - \begin{bmatrix} x \\ f(x) \end{bmatrix} \right) \leq 0.$$

Conclude that the hyperplane defined by normal vector $(\nabla f(x), -1)$ supports $\textbf{epi}\, f$ at the boundary point $x, f(x)$.

3.3 Perspective of a function and epigraph

The perspective of a function $f : \mathbf{R}^n \to \mathbf{R}$ is the function $g : \mathbf{R}^{n+1} \to \mathbf{R}$ defined by $g(x, t) = tf(x/t)$, with domain $\textbf{dom}\, g = \{(x, t) \mid x/t \in \textbf{dom}\, f, t > 0\}$. We show that the perspective operation preserves convexity using epigraphs and the perspective mapping.

For $t > 0$, show that a point (x, t, s) in $\textbf{epi}\, g$ if and only if $(x/t, s/t) \in \textbf{epi}\, f$.

Then, recognize that $\textbf{epi}\, g$ is the inverse image of $\textbf{epi}\, f$ under the perspective mapping, and conclude that $\textbf{epi}\, g$ is convex, therefore g is convex.

3.4 Linear fractional mapping and conditional probabilities

The linear fractional function is the composition of the perspective function with an affine function. Let $g : \mathbf{R}^n \to \mathbf{R}^{m+1}$ be an affine function, i.e.

$$g(x) = \begin{bmatrix} A & b \\ c^\intercal & d \end{bmatrix} \begin{bmatrix} x \\ 1 \end{bmatrix},$$

where $A \in \mathbf{R}^{m \times n}$, $b \in \mathbf{R}^m$, $c \in \mathbf{R}^n$, and $d \in \mathbf{R}$. Then the linear fractional function is $f = P \circ g$, where P is the perspective map, so

$$f(x) = \frac{Ax + b}{c^\intercal x + d}, \textbf{dom}\, f = \{x \mid c^\intercal x + d > 0\}.$$

Note that when $c = 0$ and $d > 0$, f becomes an affine function and $\textbf{dom}\, f$ is all of $\mathbf{R}^n$, so we can consider affine and linear functions as special cases of linear fractional functions.

We will use the convexity of linear fractional mapping to show that the set of conditional probabilities is convex.

Consider random variables U and V that take on values in $\{1, \ldots, n\}$ and $\{1, \ldots, m\}$, respectively, and let p_{ij} denote the joint probability $\textbf{prob}(u = i, v = j)$. Let $C \subseteq \mathbf{R}^{nm}$ denote the set of all possible joint probabilities of (U, V), so C is the probability simplex in $\mathbf{R}^{nm}$, which is convex, with each vertex corresponding to the joint probability distribution having $p_{ij} = 1$ for each (i, j).

Then the conditional probability is

$$f_{ij} = \mathbf{prob}(u = i \mid v = j) = \frac{p_{ij}}{\sum_{k=1}^{n}} p_{kj}.$$

Let D denote the set of all conditional probabilities. Show that D is convex.

4 Convex functions (1 point)

4.1 Geometric mean

Show that the geometric mean $f(x) = (\prod_{i=1}^{n} x_i)^{1/n}$ is concave on $\mathbf{dom}\, f = \mathbf{R}^n_{++}$ by showing its Hessian $\nabla^2 f(x)$ is negative-semidefinite. (Hint: this is similar to how we showed the convexity of log-sum-exp.)

4.2 Sum of largest elements

Show the sum of r largest elements, defined by $f(x) = \sum_{i=1}^{r} x_{[i]}$, where $x_{[i]}$ is the ith largest element of $x \in \mathbf{R}^n$, is a convex function. Hint: use pointwise maximum.

4.3 Entropy and perspectives of negative log

Recall that $\log$ is concave, so $f(x) = -\log x$ on $\mathbf{R}_{++}$ is convex.

1. The *relative entropy* of two scalars $(x, t) \in \mathbf{R}^2_{++}$ is $g(x, t) = t \log \frac{t}{x}$. Show this is a convex function. (Hint: perspective on negative log.)

2. Show that the relative entropy of two vectors, $u, v \in \mathbf{R}^n_{++}$,

$$g(u, v) = \sum_{i=1}^{n} u_i \log \frac{u_i}{v_i},$$

is convex in (u, v).

3. Show that the *Kullback-Leibler divergence* (KL-divergence) between $u, v \in \mathbf{R}^n_{++}$, given by

$$D_{\mathrm{kl}}(u, v) = \sum_{i=1}^{n} u_i \log \frac{u_i}{v_i} - u_i + v_i$$

is convex.

Note that the KL-divergence satisfies $D_{\mathrm{kl}}(u, v) \geq 0$ and $D_{\mathrm{kl}}(u, v) = 0$ if and only if $u = v$, so it can be used as a measure of deviation between two positive vectors. When applied to probability vectors, i.e. u and v satisfy $\mathbf{1}^\mathsf{T} u = \mathbf{1}^\mathsf{T} v = 1$, the KL-divergence and the relative entropy are the same.

4. Show the *normalized entropy* function,

$$h(u) = -\sum_{i=1}^{n} u_i \log \frac{u_i}{\sum_{k=1}^{n} u_k},$$

is concave in u. (Hint: take $v_i = \mathbf{1}^\mathsf{T} u$ in the relative entropy function.) Note the normalized entropy is equal to the entropy scaled by a constant, $h(u) = \mathbf{1}^\mathsf{T} u H(z)$, where z is the normalized version of u, $z_i = \frac{u_i}{\sum_{k=1}^{n} u_k}$, and $H(z) = -\sum_{i=1}^{n} z_i \log z_i$ is the entropy function over probability vectors z.

5 CVXPY practice (2 points)

(Problem 5 of homework 1 from [3].)

As introduced in class, CVX implements disciplined convex programming (DCP), a systematic way of specifying and recognizing convex functions using compositional rules. This allows us to quickly formulate convex optimization problems without worrying about the technicalities of solving a convex optimization problem. For large scale problems that needs efficiency and speed, other convex optimization frameworks such as MOSEK will work better, but may require specifications of the optimization problem on a more detailed level. So, for our purpose, to quickly setup and solve diverse types of problems, CVX is a great tool. Take this exercise to quickly get your hands on CVX and solve some optimization problems.

CVX is accessible in several languages, but CVXPY for python is strongly recommended. The link for download and some tutorials is here: `http://www.cvxpy.org/`.

5.1 Least squares

Get it set up on your laptop or on the cloud and make sure you can solve the least squares $\min_\beta \|y - X\beta\|_2^2$ for an arbitrary vector y and matrix X. Check your answer with the closed-form solution $\beta^* = (X^\intercal X)^{-1} X y$.

5.2 Support vector machine

Support vector machine is a way to find the classification for a set of data points. When there are two classes, for example, it finds a boundary that maximizes the margin between points in the two classes. We explore this a bit using convex optimization, mainly as an exercise to get familiar with CVX.

Given labels $y \in \{-1, 1\}^n$, and a feature matrix $X \in \mathbf{R}^{n \times p}$, with rows $x_1, \ldots, x_n$, the support vector machine (SVM) problem is the following.

$$\begin{array}{lll} \min\limits_{\beta, \beta_0, \zeta} & \frac{1}{2}\|\beta\|_2^2 + C \sum_{i=1}^n \zeta_i & \\ \text{s.t.} & \zeta_i \geq 0, & i = 1, \ldots, n, \\ & y_i(x_i^\intercal \beta + \beta_0 \geq 1 - \zeta_i, & i = 1, \ldots, n \end{array} \tag{1}$$

1. Load the training data in `xy_train.csv`. This is a matrix of $n = 200$ row and 3 columns. The first two columns give the first $p = 2$ features, and the third column gives the labels. Using CVX, solve the SVM problem with $C = 1$. Report the optimal criterion value, and the optimal coefficients $\beta \in \mathbf{R}^2$ and intercept $\beta_0 \in \mathbf{R}$.

2. The SVM solution defines a hyperplane
$$\beta_0 + \beta^\intercal x = 0,$$
which serves as the decision boundary for the SVM classifier. Plot the training data and color the points from the two classes differently. Draw the decision boundary on top.

3. Define $\tilde{X} \in \mathbf{R}^{n \times p}$ to have rows $\tilde{x}_i = y_i x_i$, $i = 1, \ldots, n$, and solve using CVX the following problem
$$\begin{array}{ll} \min\limits_{w} & -\frac{1}{2} w^\intercal \tilde{X} \tilde{X}^\intercal w + \mathbf{1}^\intercal w \\ \text{s.t.} & 0 \leq w \leq C_1, \\ & w^\intercal y = 0 \end{array} \tag{2}$$

Report the optimal criterion value. It should match that from part 1. Also report $\tilde{X}^\intercal w$ at optimal w. This should match the optimal β from part 1. Note: this is an example of duality, which will be discussed in week 4.

4. Investigate many values of the cost parameter $C = 2^a$ as a varies from -5 to 5. For each a, solve the SVM problem, form the decision boundary, and calculate the misclassification error on the test data in `xy_test.csv`. Make a plot of misclassification error (y-axis) versus C (x-axis, in log scale.)

5.3 Disciplined convex programming

Let us practice to specify valid convex problems in disciplined convex programming. Recall from class that certain ways of specifying a convex function may make it easier to be recognized as a convex function by DCP than others. See the website `http://dcp.standord.edu` for info on DCP. For each of the following expression, first explain why they define a convex set. Then, give an equivalent DCP expression along with a brief explanation of why the DCP expression is equivalent to the original. To test whether your specification is recognized as a convex function by DCP, use the analyzer at this website `http://dcp.stanford.edu/analyzer`.

1. $\|(x, y, z)\|_2^2 \leq 1$
2. $\sqrt{x^2 + 1} \leq 3x + y$
3. $1/x + 2/y \leq 5$, $x > 0$, $y > 0$
4. $(x + y)^2/\sqrt{y} \leq x - y + 5$, $y > 0$
5. $(x + z)y \geq 1, x + z \geq 0, y \geq 0$
6. $\|(x + 2y, x - y)\|_2 = 0$
7. $x\sqrt{y} \geq 1, x \geq 0, y \geq 0$
8. $\log(e^{y-1} + e^{x/2}) \leq -e^x$

6 Linear matrix inequality (LMI) for stability of biomolecular dynamical systems (2 points)

6.1 Linear matrix inequality (LMI) and stability

1. Define $A(x) = x_1 A_1 + \cdots + x_m A_m$, where $A_i, B \in \mathbf{S}^p$. $A(x) \preceq B$ is called a linear matrix inequality (LMI) in x. Show that the solution set $\{x : A(x) \preceq B\}$ is convex. (Hint: consider the function $f : \mathbf{R}^n \to \mathbf{S}^m$ given by $f(x) = B - A(x)$ and its inverse image.)

2. *Lyapunov inequality for local stability*. In 1890, Lyapunov established the following result: for a linear time invariant dynamical system
$$\frac{d}{dt}x = Ax$$
where $A \in \mathbf{R}^{n \times n}$, it is stable, i.e. all trajectories converge to zero, if and only if there exists a positive definite matrix $P \in \mathbf{S}^n_{++}$ such that
$$A^\intercal P + PA < 0.$$
The linear matrix inequality in P of the above form is called a *Lyapunov inequality*.

   It is also well-known that the above system is stable if and only if the real part of the eigenvalues of A are all negative. A matrices with this property is called *Hurwitz*.

Check that, for $n = 2$, the condition for A to have a solution to the Lyapunov inequality and for A to be Hurwitz are the same. You can check this by algebraic manipulations or check this by computational scanning.

6.2 Special structure of biomolecular reaction networks

Biological organisms exhibit fantastically diverse and versatile behaviors, yet they maintain a resilient state of livelihood that is stable and robust to disturbances. Underneath the hood, cells have millions of complex biomolecules interacting through thousands of chemical reactions that, albeit bewilderingly complicated, maintains a homeostasis and adapts towards certain goals. One marvelous fact about biomolecular systems in cells is that they achieve such stability and robustness without intricate and precise machinery like our computers, but instead only rely on floppy biomolecules' random collisions that form noisy and bursty chemical reactions. How could such stable and robust behaviors come out of such unreliable components?

We study this briefly through the perspective of the biomolecular systems' stability despite uncertainty in the parameters, and the answer comes out to be in terms of linear matrix inequalities!

This problem is based on results in [4].

1. Generically, biomolecular systems exhibit nonlinear behavior. When studying a nonlinear dynamical system, we write the system in the following form:

$$\frac{d}{dt}x = f(x),$$

where $f : \mathbf{R}^n \to \mathbf{R}^n$ is some generic function satisfying certain regularity conditions such that the solution over all $t > 0$ exists.

To study the stability of such a nonlinear system, it is usually hard to conclude whether the system is globally stable, i.e. converging to 0 as $t \to \infty$ from arbitrary initial conditions. On the other hand, if we already know a fixed point, i.e. a point $x^* \in \mathbf{R}^n$ such that $f(x^*) = 0$, then we can study whether this fixed point is locally stable by linearizing the system around this fixed point. Define $A = \frac{d}{dx}f(x^*)$, the derivative of f evaluated at x^*, we obtain the first order approximation of the dynamics in terms of variable $\delta x = x - x^*$:

$$\frac{d}{dt}\delta x = A\delta x.$$

Then the fixed point x^* is locally stable, i.e. starting from a point $x = x^* + \delta x$ very close to x^* then $x(t)$ will converge to x^* over time, if A is Hurwitz.

Since A is Hurwitz is equivalent to A has a solution to the Lyapunov inequality, we can easily test this using CVX.

Consider the following system, which is adapted from the heat shock response system in bacteria (see [2] for more details on the biology). Linearize it by hand, and test for a bunch of parameter values to see that the fixed point seems always stable. (Note that the parameters should all be positive.)

$$\frac{d}{dt}x_\sigma = k_p - k_{pr}x_\sigma x_D x_F$$
$$\frac{d}{dt}x_{mD} = k_{mD}x_\sigma - k_{md}x_{mD}$$
$$\frac{d}{dt}x_{mF} = k_{mF}x_\sigma - k_{md}x_{mF}$$
$$\frac{d}{dt}x_D = k_p x_{mD} - k_{pd}x_D$$
$$\frac{d}{dt}x_F = k_p x_{mF} - k_{pd}x_F$$
$$\frac{d}{dt}x_{Pun} = k_{un} - k_f x_{Pun}x_D$$

2. The exploration of the system above may make you wonder: could it be that the system is stable for all parameters? Indeed, this is quite often the case for biomolecular systems. For example, the simplest dynamics of a biomolecule's concentration is that it is produced at a constant rate and degraded in first order,

$$\frac{d}{dt}x = \mu - \gamma x,$$

where $x \in \mathbf{R}_{++}$ is a scalar, $\mu > 0$ is a production rate constant, and $\gamma > 0$ is a degradation rate constant. It is easy to see that this system is globally stable for all parameter values of μ and γ. So maybe biological systems tend to be stable despite parameter variations because of some special structure?

Biological systems have a special structure that all quantities are positive! The variables are concentrations of biomolecules, which is positive. They change by reactions that produce or degrate them, and the flux of these reactions is also positive. So we can always write a biological system in the following birth-death form:

$$\frac{d}{dt}x_i = f_i(x) = f_i^+(x) - f_i^-(x),$$

where $x \in \mathbf{R}^n_{++}$ is the concentration of biomolecules involved, $f_i^+ : \mathbf{R}^n_{++} \to \mathbf{R}_{++}$ is the rate of production of x_i, positive, and similarly $f_i^- : \mathbf{R}^n_{++} \to \mathbf{R}_{++}$ is the rate of degradation of x_i, also positive.

Motivated by all the quantities being positive, we could take log over these variables and consider fold change, rather than linear difference. For a given fixed point x^*, take $\tilde{\delta}x_i = \frac{x_i - x_i^*}{x_i}$ to be the fold-change of x in the ith coordinate, relative to the fixed point. Then, in terms of first order approximation, rather than the additive difference corresponding to linear derivative, we have multiplicative difference corresponding to log derivatives.

Show that

$$\frac{d}{dt}\tilde{\delta}x = \mathrm{diag}(\tau^*)^{-1}\Big(H^+ - H^-\Big)\tilde{\delta}x = \mathrm{diag}(\tau^*)^{-1}H\tilde{\delta}x,$$

where $H_{ij}^\pm = \frac{\partial \log f_i^\pm}{\partial \log x_j}$ evaluated at x^* is the reaction order (or log derivative) of the production or degradation flux of x_i to x_j, and $\tau_i^* = \frac{x_i^*}{f_i^\pm(x^*)}$ (note $f_i^+(x^*) = f_i^-(x^*)$) is the timescale of x_i's turnover. $\mathrm{diag}(\tau^*)$ is a diagonal matrix with τ^* on the diagonal entries.

Show the above is true using chain rule of calculus.

3. Compared to the additive linearization where the dynamics is just one A matrix, the above fold-change linearization decomposes the dynamics as the product of two matrices: $\mathrm{diag}(\tau^*)^{-1}H$. The parameters that tend to change and are uncertain, such as concentrations and reaction rates, are contained in τ^*, while H contains reaction orders, which tend to vary much more slowly or are constant.

   Indeed, the reaction orders are defined by log derivatives, which gets the "exponent". For example, if $f(x,y) = kx^a y^b$, then $\frac{\partial \log f}{\partial \log x} = a$, and $\frac{\partial \log f}{\partial \log y} = b$. The log derivative only gets the exponent, ignoring the rate constant in front.

   Show that the H matrix for the heat shock system from part 1 is the following:

$$H = \begin{bmatrix} -1 & 0 & 0 & -1 & -1 & 0 \\ 1 & -1 & 0 & 0 & 0 & 0 \\ 1 & 0 & -1 & 0 & 0 & 0 \\ 0 & 1 & 0 & -1 & 0 & 0 \\ 0 & 0 & 1 & 0 & -1 & 0 \\ 0 & 0 & 0 & -1 & 0 & -1 \end{bmatrix}.$$

4. *Diagonal stability of a matrix.* Given that the fold change linearization yields a decomposition of the dynamics into two parts, the diagonal matrix containing uncertain timescales $\mathrm{diag}(\tau^*)$, and the structural reaction order matrix H, we naturally want to ask, could the stability despite parameter variations in biology be due to stability that only depends on H despite all possible values of τ^*? This means, could it be that the matrix $\tilde{A} = \mathrm{diag}(\tau^*)H$ is stable for all τ^*? This would imply that the system is stable in a structural sense, regardless of parameter variations.

   Just like A is stable corresponds to having a solution to the Lyapunov inequality, there is also a similar LMI for H is structurally stable, i.e. stable despite left-multiplication by any diagonal matrix with positive entries. A sufficient condition is the following, which is called *diagonal stability*: there exists a positive *diagonal* matrix P such that

$$H^\intercal P + PH < 0.$$

   Use CVX to test the H matrix from the heat shock example is indeed diagonal stable, i.e. find a positive diagonal P such that the Lyapunov inequality holds for H.

   This shows that fixed points of the heat shock system is locally stable for all variations in the parameters.

References

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