SC3.316: Mathematical Methods in Biology
Final solutions (Fall 2024)

1. (10 points) Show that complex balanced dynamical systems are quasi-thermodynamic.

Solution:

Suppose the mass-action system possesses a complex balanced positive equilibrium c^*. This implies that

$$\sum_{\mathcal{R}_{\to y}} k_{y'\to y} {c^*}^{y'} = \sum_{\mathcal{R}_{y\to}} k_{y\to y'} {c^*}^{y} \tag{1}$$

for every complex y. (1 mark)

Let $\mu(c) = \log(c) - \log(c^*)$.

$$\begin{aligned}(\log(c) - \log(c^*)) \cdot f(c) &= \sum_{y\to y' \in E} k_{y\to y'} c^y (y' - y)\mu(c) \\ &= \sum_{y\to y' \in E} k_{y\to y'} {c^*}^{y} e^{y\mu(c)} (y'\mu(c) - y\mu(c))\,(1\,\text{mark})\end{aligned}$$

Recall the property of exponential function $e^x(x' - x) \leq e^{x'} - e^x$ with equality iff $x = x'$. (2 marks)

This implies that

$$\begin{aligned}(\log(c) - \log(c^*)) \cdot f(c) &= \sum_{y\to y' \in E} k_{y\to y'} {c^*}^{y} e^{y\mu(c)} (y'\mu(c) - y\mu(c)) \\ &\leq \sum_{y\to y' \in E} k_{y\to y'} {c^*}^{y} (e^{y'\mu(c)} - e^{y\mu(c)}) \\ &= \sum_{y\in\mathcal{C}} e^{y\mu(c)} \left[\sum_{\mathcal{R}_{\to y}} k_{y'\to y} {c^*}^{y'} - \sum_{\mathcal{R}_{y\to}} k_{y\to y'} {c^*}^{y}\right] \\ &= 0\,(3\,\text{marks})\end{aligned} \tag{2}$$

with equality holding iff $(y - y_0) \cdot \mu(c)$ for all $y \in C^*$.

We still need to show that the dynamical system is quasi-static, i.e., show that the set of equilibria is identical to the set $E = \{c \in \mathbb{R}^S_{>0} : \log(c) - \log(c^*) \in S^\perp\}$.
If c is an equilibrium, then we have equality in Equation 2. This implies that $\log(c) - \log(c^*) \in S^\perp$. (1 mark)

Conversely, if $\log(c) - \log(c^*) \in S^\perp$, then $y \cdot \mu(c) = y' \cdot \mu(c)$ for every $y \to y' \in E$. Note that

$$
\begin{aligned}
f(c) &= \sum_{y\in\mathcal{C}} \left[\sum_{\mathcal{R}_{\to y}} k_{y'\to y} c^{y'} - \sum_{\mathcal{R}_{y\to}} k_{y\to y'} c^{y} \right] y \\
&= \sum_{y\in\mathcal{C}} \left[\sum_{\mathcal{R}_{\to y}} k_{y'\to y} c^{*y'} e^{y'\mu(c)} - \sum_{\mathcal{R}_{y\to}} k_{y\to y'} c^{*y} e^{y\mu(c)} \right] y \\
&= \sum_{y\in\mathcal{C}} e^{y\mu(c)} \left[\sum_{\mathcal{R}_{\to y}} k_{y'\to y} c^{*y'} - \sum_{\mathcal{R}_{y\to}} k_{y\to y'} c^{*y} \right] \\
&= 0 \,(2\,\text{marks})
\end{aligned}
\tag{3}
$$

where the second-last step follows from the fact that $y\mu(c) - y'\mu(c)$.

2. (5 points) Consider the following dynamical system

$$
\begin{aligned}
3X + 2Y &\xrightarrow{k_1} 4X + 3Z \\
2X + Y &\xrightarrow{k_2} 3Y \\
2X + Z &\xrightarrow{k_3} 4X + Y
\end{aligned}
$$

Write the dynamical system generated by the reaction network above in the following form: $\frac{dc}{dt} = YA_k\Psi$, where Y, A_k, Ψ denote the usual symbols used in the class and $c = (x, y, z)^T$ denotes the vector of concentrations corresponding to the species X, Y, Z.

Solution:

The dynamical system can be written as

$\begin{pmatrix} \dot{x} \\ \dot{y} \\ \dot{z} \end{pmatrix} = YA_k\Psi$ where

$Y = \begin{pmatrix} 3 & 4 & 2 & 0 & 2 & 4 \\ 2 & 0 & 1 & 3 & 0 & 1 \\ 0 & 3 & 0 & 0 & 1 & 0 \end{pmatrix}$, (2 marks)

$A_k = \begin{pmatrix} -k_1 & 0 & 0 & 0 & 0 & 0 \\ k_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -k_2 & 0 & 0 & 0 \\ 0 & 0 & k_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -k_3 & 0 \\ 0 & 0 & 0 & 0 & k_3 & 0 \end{pmatrix}$, (2 marks)

$\Psi = \begin{pmatrix} x^3y^2 \\ x^4z^3 \\ x^2y \\ y^3 \\ x^2z \\ x^4y \end{pmatrix}$ (1 marks)

3. (10 points) Consider a deficiency zero reaction network whose dynamics is given by $\frac{dx}{dt} = YA_k\Psi$, where Y, A_k, Ψ denote the usual symbols. Then show that $\ker(\mathrm{YA_k}) \subseteq \ker(\mathrm{A_k})$.

Solution:

Suppose that x is a member of $\ker(\mathrm{YA_k})$, i.e., $x \in \ker(\mathrm{YA_k})$. We will show that $x \in \ker(\mathrm{A_k})$. (2 marks)

Since $\mathrm{kerYA_kx} = 0$, we have $A_k x \in \ker(\mathrm{Y})$. (2 marks)

Note that $A_k x = \sum_{y \to y' \in R} k_{y \to y'} x_y (\omega_{y'} - \omega_y)$. Therefore $A_k x \in \mathrm{span}(\Delta)$ and hence $A_k x \in \mathrm{kerY} \cap \mathrm{span}(\Delta)$. (4 marks)

Since $\delta = 0$, we have $\mathrm{kerY} \cap \mathrm{span}(\Delta) = \{0\}$. (1 mark)

This implies that $A_k x = 0$ and hence $x \in \ker(\mathrm{A_k})$. (1 mark)

4. (10 points) Show that the following holds:
   (a) (5 points) $\mathrm{span}(\Delta) = \mathrm{span}(\Delta_{\to})$.
   (b) (5 points) For a reaction network having n complexes and ℓ linkage classes, we have $\dim(\mathrm{span}(\Delta)) = \dim(\mathrm{span}(\Delta_{\to})) = n - \ell$.

Solution:

(a) Note that we have $\mathrm{span}(\Delta_{\to}) \subseteq \mathrm{span}(\Delta)$. (1 mark)
It suffices to show that $\mathrm{span}(\Delta) \subseteq \mathrm{span}(\Delta_{\to})$ or equivalently $(\Delta) \subseteq \mathrm{span}(\Delta_{\to})$. (1 mark)
Suppose that $\omega_{y'} - \omega_y \in \Delta$. Then $y \sim y'$. We have the following cases:
   1. If $y = y'$, then $\omega_{y'} - \omega_y = 0$ which lies in $\mathrm{span}(\Delta_{\to})$. (1 mark)
   2. If y and y' are directly linked, then either $y \to y' \in E$ or $y' \to y \in E$. In either case, $\omega_{y'} - \omega_y \in \mathrm{span}(\Delta_{\to})$. (1 mark)
   3. If there is a sequence of $y(1), y(2), y(3), ..., y(k) \in \mathcal{C}$ such that $y \leftrightarrow y(1) \leftrightarrow y(2) \leftrightarrow \cdots y(k) \leftrightarrow y'$. Then the vectors $\{\omega_{y'} - \omega_{y(k)}, \omega_{y(k)} - \omega_{y(k-1)} \cdots \omega_{y(1)} - \omega_y\}$ are members of $\mathrm{span}(\Delta_{\to})$ and so is their sum $\omega_{y'} - \omega_y$. (1 mark)

(b) Let $L^1, L^2, \cdots L^\ell$ be the linkage classes of the network and for $\theta = 1, 2, 3, ..., \ell$ let

$$\Delta^\theta = \{\omega_{y'} - \omega_y \in \mathbb{R}^{\mathcal{C}} : y, y' \in L^\theta\} \tag{4}$$

Then $\Delta = \sum_{\theta=1}^{\ell} \Delta^\theta$ and $\mathrm{span}(\Delta) = \mathrm{span}(\Delta^1) + \mathrm{span}(\Delta^2) + \cdots \mathrm{span}(\Delta^\ell)$. (2 mark)
Let n_θ be the number of complexes in linkage class L^θ and let the complexes in that linkage class be denoted by $y_1, y_2, ..., y_{n_\theta}$. Then any number Δ^θ can be written as a linear combination of the set $\{\omega_{y_2} - \omega_{y_1}, \omega_{y_3} - \omega_{y_1}, \cdots, \omega_{y_{n_\theta}} - \omega_{y_1}\}$. (2 mark)

Therefore $\dim(\mathrm{span}(\Delta^\theta)) = \mathrm{n}_\theta - 1$ and $\dim(\mathrm{span}(\Delta)) = \sum_{\theta=1}^{\ell} (\mathrm{n}_\theta - 1) = \mathrm{n} - \ell$. (1 mark)

5. (5 points) State the Shinar-Feinberg criterion for a dynamical system to exhibit absolute concentration robustness.

Solution:

Consider a mass-action system that admits a positive equilibrium.(1 mark)

Suppose that the deficiency of the underlying network is one. (2 mark)

If there exists two non-terminal complexes that differ *only* in species s, then the system has absolute concentration robustness with respect to species s. (2 mark)

6. (10 points) Consider the following reaction network:

$$X + 2Y \xrightarrow{k_1} 3Y$$
$$Y \xrightarrow{k_2} X$$
$$X + Y \underset{k_4}{\overset{k_3}{\rightleftharpoons}} Z$$

- Does the above network satisfy the conditions of the absolute concentration robustness theorem with respect to all three species? (5 marks)
- Is there absolute concentration robustness in any species? Justify. (5 marks)

Solution:

- The deficiency of the reaction network $\delta = n - l - s = 6 - 3 - 2 = 1$. (1 mark)

  The two non-terminal complexes Y and $X + Y$ differ in the species X. The two non-terminal complexes $X + Y$ and $X + 2Y$ differ in the species Y. (2 marks)

  So it has satisfies the conditions of the absolute concentration robustness theorem with respect to species X and Y. (2 marks)

- According to the absolute concentration robustness theorem, there is absolute concentration robustness in species X and Y. (2 marks)

  Moreover, we show that there is absolute concentration robustness in species Z. The dynamical system corresponding to the above network is given by

$$\dot{x} = -k_1xy^2 + k_2y - k_3xy + k_4z$$
$$\dot{y} = k_1xy^2 - k_2y + k_3xy - k_4z$$
$$\dot{z} = k_3xy - k_4z$$

  Solving for steady-state gives $k_3xy = k_4z$ and $k_1xy^2 = k_2y$. (2 marsk)
  This implies $z^* = \frac{k_2k_3}{k_1k_4}$. This implies that there is absolute concentration robustness with respect to species Z. (1 mark)

7. Consider the following reaction network:

$$A + M \rightleftharpoons X$$
$$B + N \rightleftharpoons Y$$
$$Y \to 2A + N$$
$$B + X \rightleftharpoons Z$$
$$Z \to R + M$$

- Draw the species-reaction graph corresponding to the reaction network above. (10)
- Does the fully open extension of the network above have the capacity for multiple equilibria? (5)

Solution:

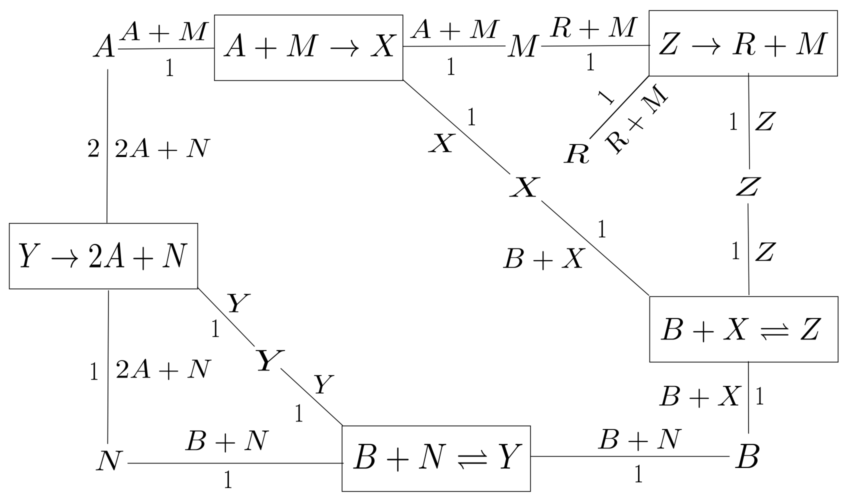

Figure 1: SR graph.

- The SR graph corresponding to the above network is shown below.
- Note that all cycles in this graphs are either o-cycles or 1-cycles. There are two e-cycles (on that visits N,Y and one that visits M,Z,X). The two e-cycles do not possess S-to-R intersection, so condition (ii) is satisfied. Therefore, the fully open extension of this network is injective, and the network does not capacity for multiple equilibria.

8. (10 points) Define the following terms:
   (a) (3 points) Dynamically equivalent systems
   (b) (3 points) Persistence
   (c) (4 points) Permanence

Solution:

1. Two mass-action systems (G, k) and $(\tilde{G}, \tilde{k})$ are said to be dynamically equivalent if the following holds true for all $x \in \mathbb{R}^n_{>0}$:
$$\sum_{y \to y' \in E} k_{y \to y'} x^y (y' - y) = \sum_{\tilde{y} \to \tilde{y}' \in \tilde{E}} \tilde{k}_{\tilde{y} \to \tilde{y}'} x^{\tilde{y}} (\tilde{y}' - \tilde{y}) \tag{5}$$
2. A dynamical system is said to be *persistent* if for any solution $x(t)$ with initial condition $x(0) \in \mathbb{R}^n_{>0}$, we have
$$\liminf_{t \to \infty} x_i(t) > 0 \tag{6}$$
for all $i = 1, 2, ..., n$.
3. A dynamical system is said to be *permanent* if for any positive stoichiometric compatibility class C there exists a compact set $M \subset C$ such that for every trajectory $x(t)$ with initial condition $x(0) \in C$, we have $x(t) \in M$ for t large enough.

9. State True or False with justification.

(a) (2 points) Union of siphons is a siphon.

(b) (2 points) Intersection of siphons is a siphon.

(c) (3 points) Union of critical sets is critical.

(d) (3 points) Any subset of a critical set is critical.

Solution:

(a) True. (1 mark)

Since the complement of a siphon is a closed set and the intersection of closed sets is closed. This implies that the union of siphons is a siphon. (1 marks)

(b) False. (1 mark)

Consider the network: $\{X + Y \to Y, X + Z \to Y\}$. The sets $\{X, Y\}$ and $\{Y, Z\}$ are siphons, but their intersection Y is not a siphon. (1 marks)

(c) False. (1 mark)

Consider the network: $\{X \to Y\}$. The sets $\{X\}$ and $\{Y\}$ are critical, but their union $\{X, Y\}$ is not critical because of the conservation law $X + Y$. (2 marks)

(d) True (1 mark)

For contradiction, suppose that T' is a non-critical subset of a critical set T. Then there is a positive conservation law $w \cdot x$ with $\mathrm{supp(W)} \subseteq \mathrm{T'} \subseteq \mathrm{T}$, contradicting that T is critical. (2 marks)

10. (15 points) Consider a reaction network. Let S denote the set of all species and let $T \subseteq S$ be a subset of species that is a minimal siphon (note that a set is minimal if it is the smallest set possessing that property. In this case, it means that there is no subset of T which is a siphon). For any set A, let $\mathrm{Cl(A)}$ denote the smallest closed set containing A. Then for every species $i \in T$, prove that $\mathrm{Cl(\{i\} \cup (S - T)) = S}$.

Solution:

Note that since T is a minimal siphon, there is no subset of it which is a siphon. (3 marks)

In addition, note that the complement of a closed set is a siphon, because if not, then there exists a reaction such that there is a species from that set in the product, and no species from that set in the reactants. This contradicts the fact that the complement of that set is closed. (6 marks)

In particular, we have $S \setminus T \subset Cl(\{i\} \cup S \setminus T)$. Therefore $S \setminus Cl(\{i\} \cup S \setminus T) \subset T$. Since $S \setminus Cl(\{i\} \cup S \setminus T)$ is a complement of a closet set, it must be a siphon. This implies that there is a siphon inside T, a contradiction. (5 marks)