Monomolecular reaction networks: flux-influenced sets and balloons

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In living cells we can observe complex network systems such as metabolic networks. Studying their sensitivity is one of the main approach for understanding the dynamics of these biological systems. The study of sensitivity is based on knocking out an enzyme which catalyzes the reaction and the responses in the concentrations of chemicals or their fluxes are observed. However, due to the complexity of the systems, it has been unclear how the network structures determine the responses of the systems. We study the network response to perturbations of a reaction rate j^* and describe which other reaction rates j' respond by nonzero reaction flux, at steady state. Nonzero responses of j' to j^* are called *flux-influence* of j^* on j'. The main and most important aspect of this analysis lies in the reaction graph approach, in which the chemical reaction networks are modeled by a directed graph. We emphasize that the analysis does not require numerical input: the require data is the graph structure only. Our specific goal here is to address a topological characterization of the flux-influence relation in the network. In fact we characterize and describe the whole set of reactions influenced by a perturbation of any specific reaction. We follow an approach by Fiedler and Mochizuki (see [FM15]), inspired by pioneering works of Feinberg [Fei87].

A *monomolecular reaction* is a chemical reaction in which any reaction j just converts one single metabolite m into another single one m'. In our approach we model a *monomolecular reaction network* as a strict directed graph Γ with a vertex set $\mathbf{M} \cup \{0\}$ and an arrow set $\mathbf{A}$. Here we call a directed graph *strict* if it has no self-loops and no two arrows have the same ordered endpoints. A dipath is any acyclic ordered sequence of alternatingly adjacent vertices and arrows. The vertices belonging to $\mathbf{M}$ are called *metabolites* and the arrows are called *reactions*. 0 is the *zero-complex* introduced by Feinberg in [Fei87]. According to Feinberg, we shall think the zero-complex as *'a complex in which the stoichiometric coefficient of every species is zero'*. 0 possesses just ingoing reactions, which are called *exit reactions*.
We skip the mathematical details of the model; see [FM15]. Suffice it to say that, under simple and reasonable assumptions, a monomolecular reaction network is precisely modeled as a strict directed graph. For nondegeneracy, we assume there exists a dipath from any metabolite m to 0.
The crucial theorem on the flux-influence relation then, according to the paper [FM15] by Fiedler and Mochizuki, reads as follows:

Theorem 1 (Fiedler&Mochizuki, 2015). *Consider any pair of reactions (j', j^*), not necessarily distinct. Then j^* flux-influences j' ($j^* \rightsquigarrow j'$) if, and only if, there exist two dipaths γ^0 and γ' such that:*
1) both dipaths emanate from m^*, the mother metabolite of j^*;
2) one of the dipaths contains j^*;
3) γ^0 terminates at vertex 0, and γ' terminates with arrow j', omitting the head vertex of j';
4) except for their shared starting vertex m^*, the two dipaths γ^0 and γ' are disjoint.

We provide here a different, more extended and precise topological characterization and description of the whole set of reactions flux-influenced by the perturbation on a specific reaction j. We give a visual description of this set, describe its structure and deepen its properties. This approach simplifies some otherwise more involved problems. Transitivity of flux-influence relation becomes in this way a simpler inclusion result on the flux-influenced sets. Some specific features of flux-influence relation arise now in a crystal clear way. See, as examples, the consequences mentioned here below at last.
For doing this, we have to introduce some new concepts which have arisen naturally in the investigation and description of the structure of the flux-influence relation. *Firstly*, we say that an outgoing reaction j from metabolite m is in the **m0-direction** if there exists a dipath γ from m to 0 containing j. We underline that this is a consistent definition due to the fact that a dipath has to be acyclic. The *second* tool is the principal and leading idea of our work: the obliged elements. We provide three equivalent definitions, to give a viewpoint as wide as possibile. The set O_0^m of **obliged elements from m to** 0 is the intersection set of *all* dipaths from m to 0. In a more graph theoretic language, we may say that this set O_0^m is the set of the cut-vertices and cut-edges (bridges) of the subnetwork which consists of all dipaths from m to 0. Finally, plainly said, this set O_0^m contains all elements of the network whose deletion renders 0 unreachable by any dipath from m. This set O_0^m has several interesting properties. It is crucial to mention one of those here: it possesses a total order. Of course any dipath from m to 0 trivially induces a natural order in the set of the obliged elements from m to

0. By acyclicity, this order does not depend on the chosen dipath. In particular we may speak about the *first, second, ...* obliged element from m to 0. *Lastly*, let $x(m)$ be the *first* obliged element from m to 0. We define the $(m, 0)$-**Balloon** B_0^m as the subnetwork reachable from m with a dipath without passing through $x(m)$. We might say that a Balloon consists of different components: for any outgoing reaction j' from m that is *not* in the $m0$-direction then the set reachable with a dipath from m starting along j', which we indicate with $R^{m,j'}$, is a subset of the $(m, 0)$-Balloon. This subset is exactly the $(m, 0)$-Balloon if m has exactly only two outgoing reactions, otherwise it is a strict subset.

Now we get to our main theorem which characterizes precisely the set flux-influenced by a perturbation over a single reaction.

Theorem 2 (Characterization of flux-influenced sets)**.** *Let j be a reaction with its mother metabolite m. Then the set $I(j)$ flux-influenced by j is characterized as follows:*

1) if j is in the $m0$-direction, then $I(j)$ consists of all the reactions in the $(m, 0)$-balloon B_0^m, and no others;

2) if j is not *in the $m0$-direction, then $I(j)$ consists of all reactions in $R^{m,j}$, namely all reactions reachable from m with a dipath starting along j, and no others.*

We underline again that the set $R^{m,j}$ described in the latter case 2, namely the set flux-influenced by a perturbation on a reaction which is *not* in the $m0$-direction, is a subset of the $(m, 0)$-balloon B_0^m.

The proof of the above result relies on a classical graph theory result: Menger's Theorem.

The following theorem and corollary arise straightforwardly from our analysis:

Theorem 3 (Inclusion of Flux-influenced sets)**.** *If j^* influences j', then $I(j^*) \supseteq I(j')$.*

Corollary 4 (Transitivity of Flux-influence relation)**.** *The flux-influence relation is a transitive relation, i.e., $j^* \rightsquigarrow j' \rightsquigarrow j''$ implies $j^* \rightsquigarrow j''$.*

Recently, Brehm and Fiedler generalized this last transitivity result to multimolecular networks, following a more algebraic approach (for this, see [BF16]).

Finally, some consequences are worth to be mentioned:

1) For any outgoing reaction from metabolite m, all flux-influence is confined to the $(m, 0)$-Balloon.

2) Single child reactions from their mother metabolite have no influence.

3) If i and j are two outgoing reactions from metabolite m, both in the $m0$-direction, then $I(i) = I(j)$.

4) If i and j are the two only outgoing reactions from m, then $I(i) = I(j)$.
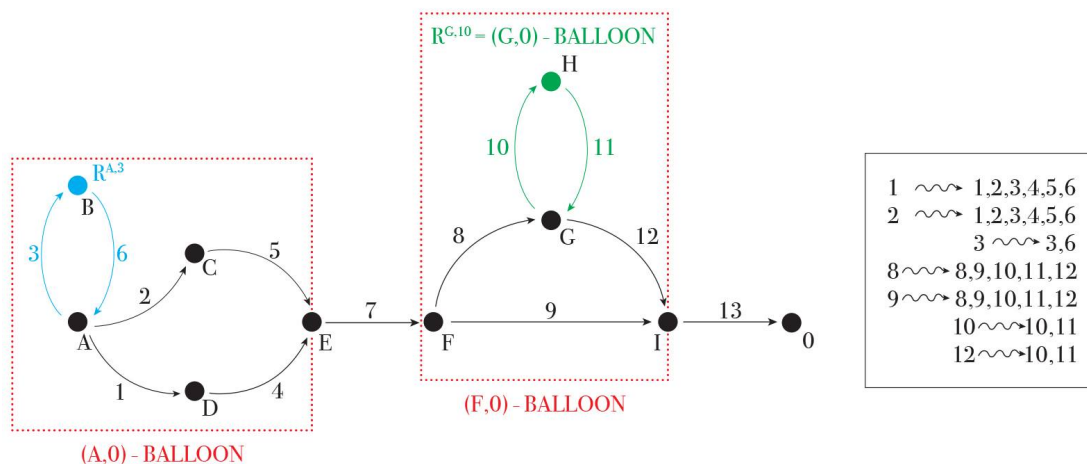

Figure 1: *In the picture, a generic monomolecular reaction network. The complete flux-influence relation is described in the square on the right. In the red squares the two main balloons in the network. The first obliged element from A to 0 is E and from F is I. Note that $I(1) = I(2) = (A, 0)$-Balloon and $I(8) = I(9) = (F, 0)$-Balloon. Note as well that $I(10) = I(12)$: since 10 and 12 are the only two outgoing reactions from metabolite G, in this case the $(G, 0)$-Balloon is just $R^{G,10}$, i.e., the set reachable with a dipath from G starting along 10.*

References

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