若手研究者インターナショナル・トレーニング・プログラム(ITP)
バイオインフォマティクスとシステムズバイオロジーの国際連携教育研究プログラム　報告書

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Title: Modelling the Robustness of Metabolic Pathways

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Report:

Introduction of laboratory

The partner laboratory is Centre for Computational Biology belonging to Mines ParisTech. The group leader is Prof. Jean-Philippe Vert who works at both MineParisTech and Curie Institute. For this international training program, I was staying in one of Prof. Jean-Philippe's office at Curie institute. Curie institute has a very nice building located in the south bank of Seine River, closed to the Luxembourg garden and the Pantheon. Jean-Philippe laboratory shares an open space with several other groups in this nice building. Members in Curie Institute are free to choose seats since each of them has a personal account for an access to all of the computers (with Linux OS) in the building. These public computers are administrated by their media center so that they always ensure a continuously upgraded and safe computational environment for the researchers. Jean-Philippe lab have group meeting once a week, machine learning class twice a week and also some other sporadic seminars. During my stay, I went to the institute by rental bike (called velib') every workday, shared different room with different people in the institute, and worked directly together with Prof. Jean-Philippe on the project. All of the members in this lab were very nice and they helped me to quickly get a hang of the study and life in Paris.

Figure 1: Curie Institute and the lobby where I had discussion with Prof. Jean-Philippe every week.

Research objective

As we know that metabolic pathways are complex systems of chemical reactions taking place in every living cell to degrade substrates and synthesize molecules needed for life. Reactions can be perturbed by, e.g., drugs or mutations in DNA. When one or a few reactions are perturbed, the

impact of this perturbation on the cell can vary widely, depending on how many other reactions are impacted in cascade. The group was recently interested in the project of modeling the robustness of metabolic pathways in cancer research. Related approaches also proposed some measures such as FBA, MOMA, EMA and Synthetic Accessibility [3] for robustness evaluation, while our motivation was to propose and implement new computational models to quantify the impact of inhibiting one or a few reactions on the global metabolic network, and to evaluate the robustness of metabolic networks based on this model. During this international collaboration, my work is to propose such a new computational model and apply it to E-coli data [2].

Graph spectrum method

Through continually discussion with Prof. Jean-Philippe and Prof. Akutsu, I proposed a new method — Graph spectrum to study the robustness of metabolic networks.

1. *Preliminaries*

During this study, a metabolic network was represented by its Laplacian graph spectrum and topological change (on reaction removal) was represented by spectral distance. This work was focused on computing spectrum distance between metabolic network and some new network, where such a new network was constructed by removing all inhibited reactions caused by knockout of a single reaction from the original one (see also Fig. 2: ⓘ). I used a narrow Cauchy-Lorentz distribution showing as follows to compute the spectral density of a network: (Fig. 2: ⓘⓥ)

$$\rho(\omega) = \mathrm{K}\sum_{i=1}^{N}\frac{r^2}{(\omega-\omega_i)^2+r^2} \qquad (1)$$

where r is a scale parameter, K is a normalization factor and $\omega_i\ (i=1,\ldots,N)$ is eigenvalues of the adjacent matrix of a graph in ascending order.

The distance between two networks with spectrum densities $\rho_1(\omega), \rho_2(\omega)$ was defined as: (Fig. 2: ⓥ)

$$\varepsilon = \sqrt{\int_0^{+\infty}[\rho_1(\omega)-\rho_2(\omega)]^2 d\omega} \qquad (2)$$

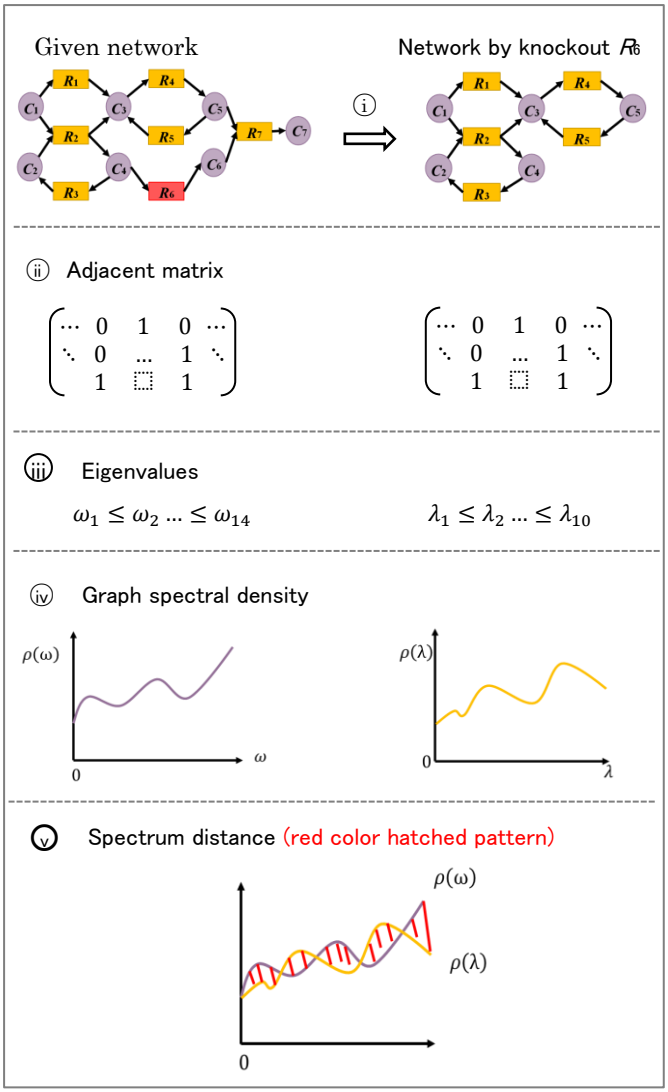

Figure 2: An outline of graph spectrum method.

2. *Program design*

In this section, I would like to introduce the major steps of this Graph spectrum method. There were five steps involved in this research: (Fig. 2 gives a simple instance of the outline.)

(i).Construct all possible networks by removing inhibited reactions and compounds caused by the knockout of some reaction in metabolic network;

(ii).Construct the adjacent matrices of the given network and each new network;

(iii).Compute the eigenvalues of these matrices;

(iv).Use formula (1) to compute the density of a spectrum between the given data and each new data;

(v).Finally, the distance between original network and each new network can be computed by following formula (2).

Experimental results & Discussion

1. *Spectrum distance results*

I applied this method to E-coli data from KEGG database and finished computing the spectrum distance between the E-coli network and some new network. Here a new network was constructed by some reaction knockout. As an illustration, Fig. 3 shows a plot of the spectrum density of E-coli network and new network constructed by reaction R00416 knockout.

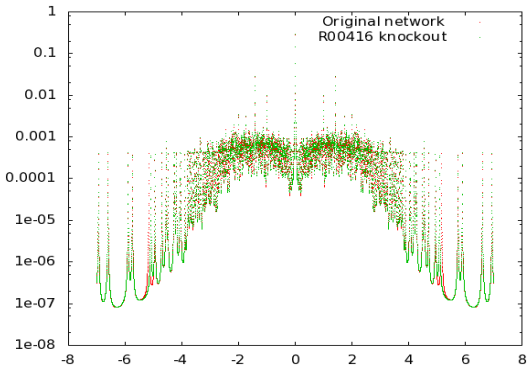

Figure 3: Plot of the spectrum density of E-coli network and R00416 knockout. Red and green dots represent E-coli data and new date with R00416 knockout, respectively.

2. *Comparison to impact degree*

I also investigated the correlation between spectrum distance and impact degree proposed by Tamura-san's recent paper [1]. The results are shown in Fig. 4. From the results, we can see that it seems to have correlation between impact degree and spectrum distance. However, there still existed some cases that large (small) impact degree corresponds to small (large) spectrum distance.

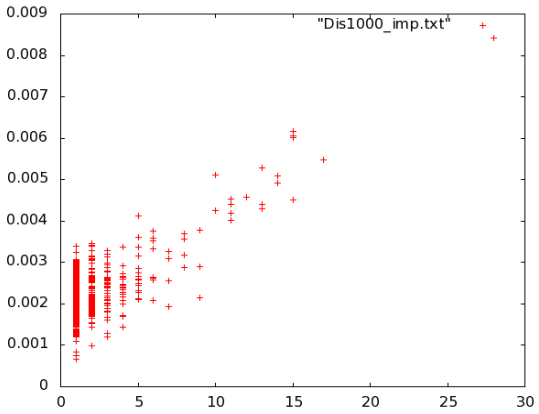

Figure 4: Result of comparison to impact degree, where x axis and y axis denote impact degree and spectrum distance

3. *Discussion*

Prof. Jean-Philippe and I discussed the reason why the above cases were obtained. We got a conclusion that in some cases, removing a large number of inhibited reactions and compounds caused by a single reaction did not change the structure of the metabolic network too much because this reaction may not play an important role in the network and vice-versa. Through this collaboration, I successfully proposed a new method to evaluate the robustness of metabolic network. Further comparison to some other existing approaches is supposed to be done to evaluate the efficiency of this method in the next step.

Some activities

There were some parties during my stay in Curie institute, some of which are organized by the school and some others are hold by the office of my living place. I joint several of them (Fig. 5: left), enjoyed the food and also had very good time with those kindly people (institute members or just people lived in the same apartment). In the weekend, I also visited some famous places in Paris, such as the Eiffel Tower (Fig. 5: top right) and the Sacre Coeru (Fig. 5: bottom right), etc.

Figure 5: Parties and travels.

Acknowledgements

First and foremost, I would like to express my sincere thanks to Prof. Akutsu for his permission of my participation to this program and valuable advice during my stay. My heartfelt thanks also go to Prof. Mamitsuka and Prof. Kanehisa for giving me this international collaboration chance. I shall extend my thanks to Prof. Jean-Philippe for his valuable comments and helpful suggestions on the project < Modelling the Robustness of Metabolic Pathways >. I would like to particularly thank the members in Jean-Philippe lab and the secretary Jennifer for their kindness, encouragement and help in my studies and life in Paris.

Figure 6: Jean-Philippe group (left), the secretary Jennifer (center) and PhD. Student Toby (right).

References

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