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 応募書類

Name: Sayaka Mizutani
Title: Analysis of drug targeting protein networks in dynamic models
Institute: Bioinformatics Center, Institute for Chemical Research, Kyoto University
Partner institute of your choice：Humboldt University in Berlin
Duration of your choice: January 7, 2014 – March 16, 2014
Report： Thanks to the financial support from the International Training Program (ITP) I was given an opportunity to visit the Theoretical Biophysics Laboratory, Humboldt University in Berlin. The Professor Edda Klipp's laboratory studies systems biology with a variety of biological interests including yeast metabolism. The lab members are dedicated to one or a few topics in groups. There were two weekly meetings, a group meeting where all members report their progresses, and a seminar where one person is given a whole hour to present his/her research. Several guests also came to the seminars. Among them the most interesting was a talk by Professor Dirk Brockmann from the Institute for Theoretical Biology, Humboldt University in Berlin about his recent publication on a world-wide epidemic model (Brockmann and Helbing, 2013). The laboratory also set up special weeks for a selected project, where the project was divided in smaller modules so that the members in a group work together to set up and archive a goal within the week. Professor Edda Klipp's laboratory provided one of the ideal research environments where postdoctoral fellows and students had close communications through which technical and biological questions were shared and solved cooperatively. During my stay I collaborated with Dr. Marcus Krantz and Dr. Max Flöttmann in studying the dynamic model of cancer-related signal transduction pathways and the effects of combinatorial use of molecular targeting drugs. In a bipartite Boolean network modeling framework *rxncon*, which has been developed in Professor Edda Klipp's laboratory (Tiger *et al.*, 2012 and Flöttmann *et al.*, 2013), a dynamic network model is defined by update rules based on a set of *reactions* and a set of *contingencies*, resulting a bipartite graph representation of the network (Figure 1). A *reaction* set is a list of reactions occurring between molecules (*e.g.* Receptor tyrosine kinase A phosphorylates Enzyme B). A *contingency* set defines constraints for the reactions to occur (*e.g.* Receptor tyrosine kinase A phosphorylates Enzyme B constraint to the state that Receptor tyrosine kinase A is bounded by Ligand C). The framework outperforms classical Boolean network models in describing signal transduction pathways because it implements protein states (*e.g.* phosphorylated) as a result of signaling events in a mechanistic way. Using the framework, it is possible to introduce specific experimental conditions in a network such as the presence or absence of outside signals. Regarding the treatment of drug resistance in cancer cells, combinatorial use of molecular targeting drugs has been gaining more attention. For example, breast cancer cells acquire resistance to trastuzumab, an *ERBB2* inhibitor, by gaining mutation in *PI3K* or *PTEN* loss, which

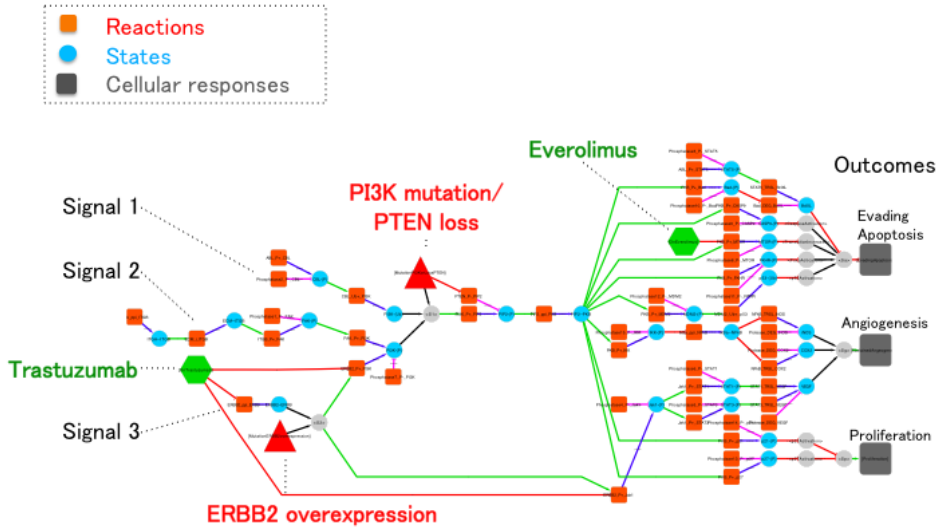

Figure 1 Regulatory network representation of breast cancer-related PI3K pathway.

can be cured by everolimus, a *mTOR/PI3K* pathway inhibitor. However, identification of ideal drug combinations requires computational approaches. The bipartite Boolean network approach may help to simulate and monitor the dynamic behaviors of network signal processing with or without alterations in specific proteins. Based on a KEGG cancer pathway map (Kanehisa et al., 2014), we constructed *reaction* lists and *contingency* lists. Final states of the pathway are defined based on the concepts of "the hallmarks of cancer" defined in Hanahan and Weinberg, 2011). In this study, three different cell states were examined; (1) normal cell, (2) cancer cell, and (3) cancer cell on anti-neoplastic molecular targeting drug(s). Breast cancer and non-small cell lung cancer models were constructed and examined with single and double mutations, and single use and combinatorial use of the drugs (Table 1). The constructed models successfully described the reasonable outcomes in respect to the conditions given. The combinatorial use of drugs described the effect of double mutations resulting in the rescue of anti-cancer cellular responses (Figure 2).

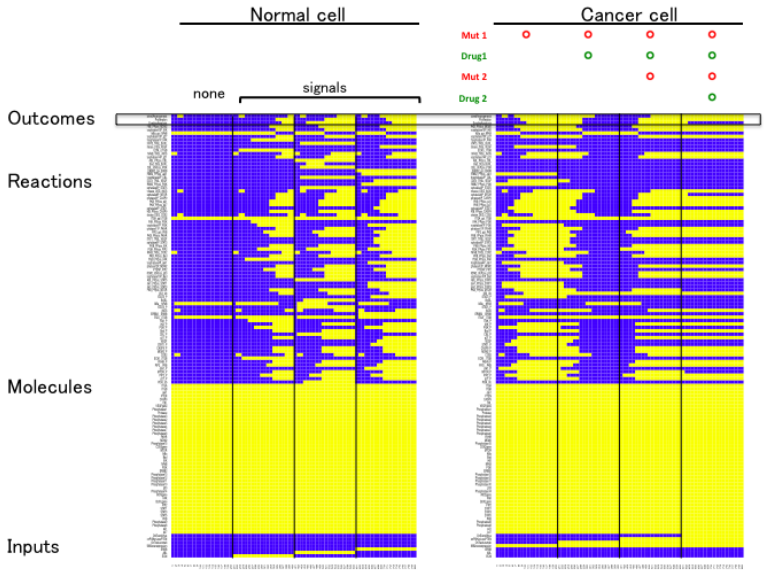

Figure 2 State transitions of breast cancer model in phosphoinositide-3-kinase (PI3K) pathway.

Table 1. Types of cancers studied

Type of cancer	Related pathway	Mutation	Drug
Breast cancer	PI3K pathway	Mut 1：*ERBB2* overexpression	Drug 1：Trastuzumab
		Mut 2：*PI3K* mutation/*PTEN* loss	Drug 2：Everolimus
Non-small cell lung cancer	PI3K pathway & MAPK pathway	Mut 1：*KRAS* mutation	Drug 1：Selumetinib
		Mut 2：*PKB* mutation	Drug 2：MK2206

Future work will be to extend to a larger network to add more drugs and targets to search for new combinations. One possibly interesting result would be how the integration of different pathways reveal the effects of signals which could propagate through multiple pathways.

Acknowledgement：
I appreciate Professor Hiroshi Mamitsuka and Associate Professor Susumu Goto for providing me a great opportunity to participate in the ITP. I also thank Professor Edda Klipp for hosting me and setting up a collaborative research. Dr. Marcus Krantz and Dr. Max Flöttmann always gave me advices in technical and biological means. Dr. Mao Tanabe from the KEGG group helped me to interpret the KEGG cancer pathway.

Reference：

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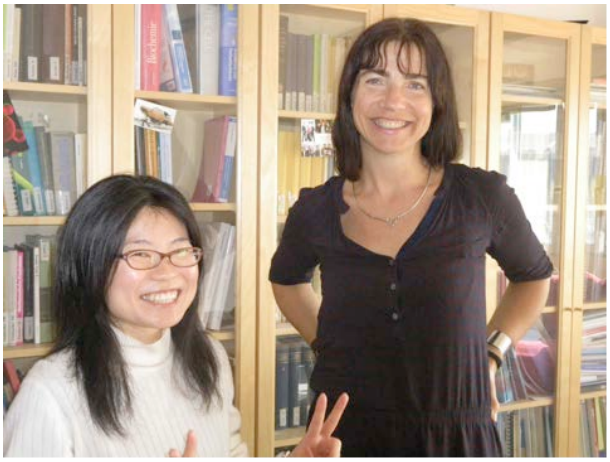
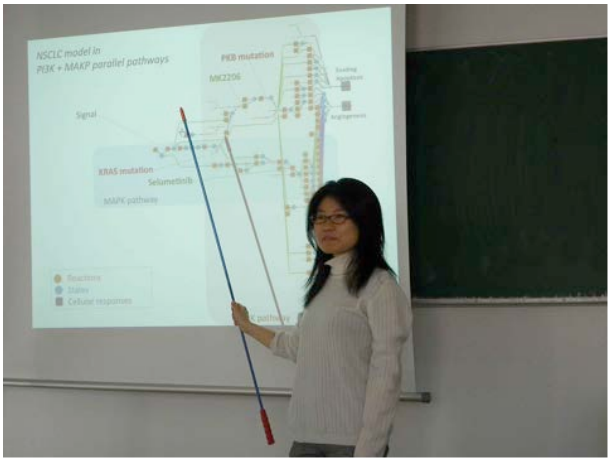


Picture with Professor Edda Klipp



Presenting my result in a laboratory's seminar