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 Berlin
Duration of your choice: January 7, 2014 – March 16, 2014

Research Objectives :

The applicant has studied publicly available pharmacological data to find significant links from the molecular side of a drug action to its phenotypic effects in the human body, the side-effects or adverse drug reactions. Previously, the applicant used a biclustering approach on drug adverse event reports to cluster medically similar adverse reactions that may be caused in the same drug depending on the patients' physiological backgrounds [Mizutani el at., 2014] (Figure 1). Furthermore, the applicant used the sparse canonical component analysis to extract significant relationships between target molecules of a drug and its out-coming side-effects. As a result, it has been inferred that molecular targets related to the occurrences of a group of side-effects are enriched in specific protein pathways (mostly signaling pathways), suggesting that drugs can exert a perturbation in the protein networks to cause unexpected adverse responses in the cell. Possible extension of the research is to use similar approaches to examine how combined uses of drugs in co-administration can affect multiple targets and how these effects are transmitted through the downstream pathways to cause side-effects [Mizutani el al., 2012] (Figure 2).

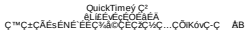

Figure 1

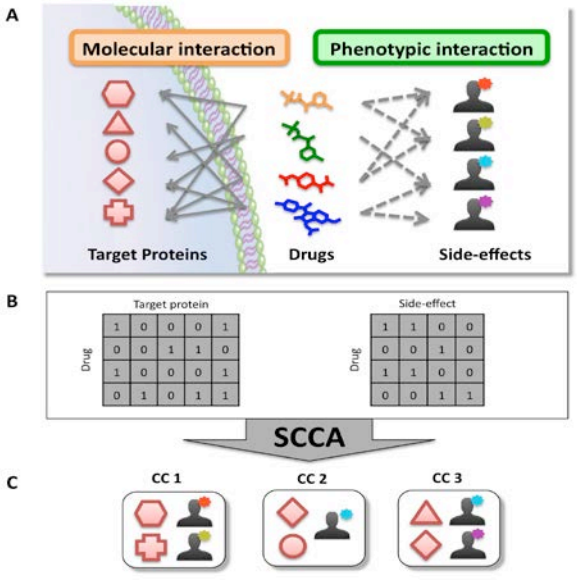

Figure 2

Recently, combinatory uses of drugs have gained more attention, because it is more common in clinical practices. Co-administration of drugs may result in unexpected drug-drug interactions (DDIs), which are conventionally defined in two categories; *pharmacokinetic* DDIs, whereby a

Plan (Continued)

drug is affecting the processes by which another drug is absorbed, distributed, metabolized, or excreted (ADME), and *pharmacodynamic* DDIs, where the effects of one drug are modified by the effect of another on its site of action or by affecting the same or cross-talking signaling pathways [Gottlieb et al., 2012]. Although the importance of pharmacodynamic DDIs through signaling pathways has been discussed [Karczewski et al., 2012], it remains mostly uninvestigated. Because many of the drug targeting molecules are involved in signaling pathways, systematic analyses of protein networks in signal transduction pathways are highly recommended.

Professor Edda Klipp's laboratory has been studying mathematical models to describe complex biological and pathological phenomena at cellular and subcellular levels and to examine their dynamic behaviors in response to extra-cellular signals. The use of mathematical models in signaling pathways, as opposed to metabolic pathways, requires the development of well-difined framework. Tiger et al. (2012) have developped a framework to code reactions and reaction states of the proteins used in bipartite boolian modeling of signaling networks.

Research Plan：

During the stay at Professor Edda Klipp's laboratory at Humboldt University, Germany, the applicant plans to study (1) dynamic modeling of signal transduction pathways and (2) the use of Systems Biology Markup Language (SBML). The applicant plans to suggest the use of their models to examine the pathway alterations within a concept of drug perturbations, that is, combinatory use of drugs may perturb the protein networks so that unexpected cellular responses may follow. For this purpose the KEGG signaling pathways are useful resources to study the functions of protein networks. During my stay at Professor Edda Klipp's laboratory I plan write the KEGG signaling pathways in the SBML format and make them usable in dynamic models.

Reference：

Gottlieb, A., Stein, G.Y., Oron, Y., Ruppin, E., and Sharan, R., INDI: a computational framework for inferring drug interactions and their associated recommendations, Molecular Systems Biology, 8:#592 (2012).

Karczewski, K.J., Daneshjou, R., and Altman, R.B., Chapter 7: Pharmacogenomics, Plos Computational Biology, 8, e1002817 (2012).

Mizutani, S., Pauwels, E., Stoven, V., Goto, S., and Yamanishi, Y., Relating drug-protein interaction network with drug side-effects. Bioinformatics 28, i522-i528 (2012).

Mizutani, S., Noro, Y., Kotera, M., and Goto, S., Pharmacoepidemiological characterization of drug-induced adverse reaction clusters towards understanding of their mechanisms, accepted to APBC 2014.

Tiger, C.F., Krause, F., Cedersund, G., Palmer, R., Klipp, E., Hohmann, S., Kitano, H., and Krants, M., A framework for mapping, visualization and automatic model creation of signal-transduction networks, Molecular Systems Biology, 8: 578 (2912).