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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Report:

During my stay at Humboldt University, I was able to interact with all the team members of Professor Edda Klipp's laboratory understanding the current team's focus within cell modeling. I attended the frequent group meetings and presentations, as well as the occasional seminar which provided an overview of the methods and issues that are currently dealt with in the yeast cell modeling. The question that was mainly asked was "How does the yeast cell respond to the stress conditions?" The yeast is a well-established model organism, and its basic functions in yeast are highly similar to those of higher eukaryotes. An integrative project was held to combine the Biosynthetic pathways, their regulations, the cell cycle, cell division, transcription regulations and transcriptional activation, signal transduction pathways, stress responses, nuclear-mitochondrial interactions (nuclear transport) and chromatin regulatory mechanisms to properly model the life cycle of the yeast cell in normal and stress conditions. Even with this simplistic model, combining the various functions to model the regulatory and predictive functions is an extreme task. This made me even further understand the complexity of nature and emphasized the need for research and understanding.

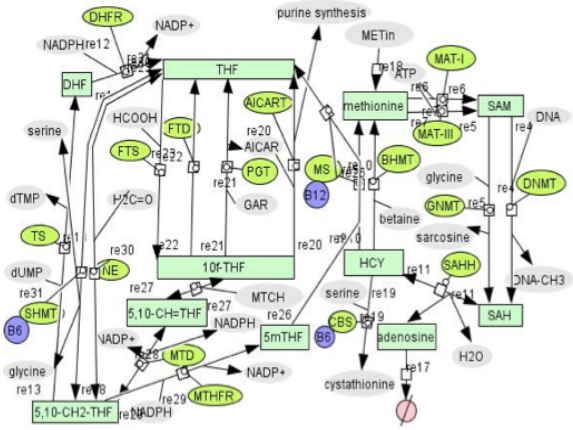
Till date, I have not worked much with yeast, but the methods that were intrigued me. Hoping to learn more about the methodology and the tools used, I joined the workshop "Modellierung Biologischer Systeme" (19 November – 29 November 2013) to eventually contribute to the cross-fertilization between the research in machine learning methods and their applications to systems biology. The workshop covered the importance of SBML, the current databases and resources, and a MATLAB and a Copasi tutorial. The intensive workshop gave an overview of the tools need to develop a SBML model through the formulations of the biochemical reactions quantified through experiments.

The topic that chose was the mathematical model of the folate metabolism (Reed et al., 2004). Using the biochemical reactions, complemented with the ODEs, I was able to create a basic model that simulated the folate metabolism system in eukaryotes. Copasi was used to optimize the parameters needed to analyze the dynamic behavior and the steady-state properties. Furthermore, a sensitivity analysis was performed to determine the values of the model variables, which included both the local and the global sensitivity analysis of my model. Optimization was performed using both Copasi and Matlab to numerically determine the properties of the complex folate metabolism model. Finally, parameter estimation was performed with the published experimental data to calibrate the represented real biological system accurately, including the analysis of enzyme kinetic experiments, and in vivo time courses of the published experiments. Using the Copasi capabilities, the experimental ODE model was represented stochastically and integrated with the CellDesigner to create a network of the FOCM (folate-mediated one carbon metabolism) reaction scheme. The generated model was rather similar to the published finding with one exception. My model was not able to generate any flux in the MTD (5,10-methylenetetrahydrofolate dehydrogenase) enzyme (Table 1). This effected the concentrations of some substrates and the fluxes of other integrative enzymes within the FOCM reaction scheme (Diagram 1-a & 1-b). Ultimately, I was not able to reproduce the exact published results, but established a firm understanding of how the current tools,

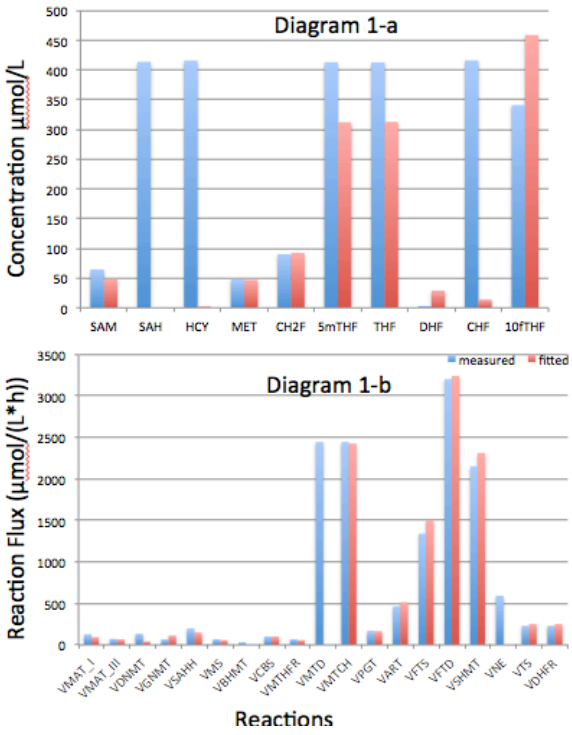
| Species | Values of the variables and fluxes | |
|---|---|---|
| | measured | fitted |
| Concentrations | in µmol/L | In µmol/L |
| SAM | 64.42 | 48.5 |
| SAH | 13.04 | 0 |
| HCY | 1.11 | 0.0086 |
| MET | 48.00 | 47 |
| CH2F | 0.90 | 0.921 |
| 5mTHF | 4.02 | 6.85 |
| THF | 8.01 | 8.85 |
| DHF | 0.03 | 0.0286 |
| CHF | 1.12 | 0.14 |
| 10fTHF | 5.93 | 8.25 |
| Reaction Fluxes | in µmol/(L*H) | in µmol/(L*H) |
| $V_{MAT\ I}$ | 127.1 | 92 |
| $V_{MAT\ III}$ | 71.35 | 66 |
| $V_{DNMT}$ | 132.43 | 41 |
| $V_{GNMT}$ | 66.05 | 112 |
| $V_{SAHH}$ | 198.5 | 149 |
| $V_{MS}$ | 66.8 | 56 |
| $V_{BHMT}$ | 31.72 | 0 |
| $V_{CBS}$ | 100 | 100 |
| $V_{MTHFR}$ | 66.77 | 56.5 |
| $V_{MTD}$ | 2444 | 0 |
| $V_{MTCH}$ | 2444 | 2426 |
| $V_{FGT}$ | 167.4 | 164.5 |
| $V_{ART}$ | 464 | 515 |
| $V_{FTS}$ | 1340 | 1500 |
| $V_{FTD}$ | 3201 | 3240 |
| $V_{SHMT}$ | 2151 | 2310 |
| $V_{NE}$ | 590 | 0 |
| $V_{TS}$ | 230 | 250 |
| $V_{DHFR}$ | 230 | 250 |

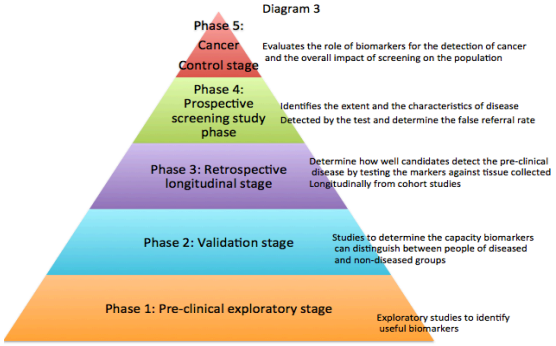
MATLAB and Copasi are used in systems biology research. I hope integrate these tools in my own research to better understand the networks of breast cancer.

Diagram 2: My CellDesigner FOCM model




I had the opportunity to present a talk emphasizes the current issues of quantification in biomarkers, entitled “Biomarker’s role in the early detection of clinically significant cancer—Is it properly quantified?” on 26 November 2013. The current viewpoint is that biomarkers are vital for disease detection in various clinical stages. Till date, a variety of cancer serum biomarkers have been proposed, yet for more accurate detection of the cancer-type and cancer-stage, several issues need to be considered, the most important being the quantitative evaluation methods of biomarkers. In the talk, I discussed the present biomarker usages under the five clinical stages (FDA approval methodology) developed by the National Cancer (Diagram 3), was followed by introducing current computational biomarker evaluation methods, including ROC Curves and diagnostic odds ratios (DOR) with its intrinsic problems. Then I briefly discussed a current list of existing cancer serum biomarkers, pointing out the present issues, mainly caused by the limitations of the current biomarker evaluation approaches. Finally, I discussed the possibility of developing new cancer evaluation approaches, which may be more statistically robust compared to the current methods in terms of the specificity of each cancer type.




Finally, I would like to thank the Program Director: Professor Hiroshi Mamitsuka for guiding me the preparation process and for giving me the opportunity for s wonderful and valuable research experience. I would also like to thank Professor Edda Klipp for accepting me to study and work with such skilled researchers and for her guidance throughout the program. Last but not least, I would like to thank the lab members of Klipp’s lab for all their help regarding to technical problems in and out of the lab.

During my stay in Edda Klipp Lab, I was also able to take advantage of the rich cultural art life in Berlin. Visiting the various famous museums and exhibitions such as the Pergamon Museum, Altes Museum, Dali Exhibition, and the Picasso Exhibition, I was able to conceptualize history facts and events into reality, and enjoy the traditions and artistic expression that resides throughout the city.

Description of pictures (Left to Right): 1. Berlin Wall Remembrance in Potzdamer Platz 2. Brandenburg Gate during the Festival of Lights exhibition 3. The iconic Christmas tree displayed in Gendarmenmarkt Weihnachtsmarkt (Gendarmenmarkt Christmas Market) 4. Egyptian exhibition in the Altes Museum 5. Hotel De Rome during the Festival of Lights exhibition 6. Charlottenburg Palace during the Weihnachtsmarkt

Description of pictures (Left to Right): 1. Hotel De Rome during the Festival of Lights exhibition 2. Egyptian exhibition in the Altes Museum 3. Brandenburg Gate during the Festival of Lights exhibition 4. Charlottenburg Palace during the Weihnachtsmarkt 5. The iconic Christmas tree displayed in Gendarmenmarkt Weihnachtsmarkt (Gendarmenmarkt Christmas Market) 6. Berlin Wall Remembrance in Potzdamer Platz

Finally, I was able to engulf the free eclectic culture of the Germans to broaden my horizons in my research and life, in general.

Artistic Expression through Music and Dance in Eberswalder Strasse Park

Vielen Dank für dieses Erlebnis.
(Thank you for this experience.)

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