Progress Report: CEq Emergence Assistant (the tool support for the CEq formal method)

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1 Aim of Research

The CEq Emergence Assistant, or `CEq-EA`, is a computerised tool for supporting the analysis along with our underlining technologies along the CEq formal method. The main purpose is to develop a feasible formal tool for studying in systems biology; i.e., aimed for building-up a comprehensive understanding and analysing for emergent properties of the target system. The tool provides not only ability to automate the CEq analysis, but also the input/output languages and selected parameters used in performing the analysis.

2 Approach/Idea

Formal properties of biological systems are still not well-defined and mostly have not been identified yet. However, in life science, there is a common meta-concept of *homeostasis*. It is an ability to maintain the system at "stable states" while adjust to changes for survival. Adjustment of multiple equilibria may capture this stability on dynamic model which is formed by contiguous changes.

In our approach, we have provided facilities from inputting as a specification to starting the analysis and finally outputting the analysed result. The input is motivated by graphical diagram of influences used widely in life-science community. Those diagrams are not only to summarise the dense textual information but also to give the system perspective view. Towards to formal approach, we have designed a specification language for declaring influences, and an ability to make their intended semantics explicit. That is required to turn the specification into intermediate representation readily for consequent symbolic computation.

The CEq, or Cascaded-Equilibria is the named after the main steps in our formal method: constructing model with *cascading* – a concept in biological signalling and analysing for *equilibria*. The cascaded signalling presents the ways of signalling may propagate towards sustained points of equilibria. We may regard that equilibria present the sustainability of catalytic effect where cascading is made by catalysts. Our focuses are on protein signalling and gene regulation systems.

Even the whole formal method is underpinned by biochemistry, but with structure in symbolic computation, it is application-free domain and can applicable to more general system.

3 Progress in this Fiscal Year (2007)

We have designed technologies needed to perform the CEq analysis, and along with tools implemented as `CEq-EA`. Along typical discrete formal method, the tool is performed as follows:

1. Start with a specification parsable by the tool; i.e., in `MIG` language (Modal Influence Graph). As an algebraic language, it consists of objects and influences as operations over them. It

not only formalises the notion of diagram of influences, but also enhances with explicit information; i.e., object states, inhibitors, and modalities for any influence. Moreover, the tool can generate *influence graph* from parsed specification for further sanity check.

2. Translate the `MIG` specification internally to a symbolic form in order to make the intended semantics of influences explicit. Let's call a formalism behind the symbolic form as $\mathbb{ARS}$ (Auto-Regulating Systems). It consists of a set of entities (object dotted states) and a relation over them as inspired by biochemical reactions.

3. Construct a Cascading Model from a given set of relations in $\mathbb{ARS}$ formalism by the mean of doing cascade between relations. The model construction is formally defined with the aspect of cascading in biochemistry; i.e., demonstrate the ways of signalling get propagated.

4. Analyse by computing equilibria on a given model, and output as a result graph. The result graph, the model graph denoting with equilibria, is generated in the form of *graphviz/dot* language which can export to numerous image file format. So far, we have defined equilibria and some apparent to be; e.g., some can collapse with the other. Those equilibria also demonstrate the sustain of catalytic effect of biochemical reactions.

All algorithms and implementation code of `CEq-EA` are designed in Java with carefully consideration of scalability and feasibility to real-world input; i.e., low polynomial complexity and low running time. In addition, A set of parameters are selected to parameterise the tool to meet with a desired analysis. Those are for modalities in specification, sanitations in symbolic computation and model construction; as well as, options for outputting the result with various kinds of equilibria indications. Currently, we provide a web interface for performing an analysis interactively with a set of typically used parameters. It is available at `http://cascade.jaist.ac.jp`.

4 Future Direction

In next step, we are aiming to apply the CEq analysis to study other well-known model organisms, and targeting on the methodology in analysing a larger system; e.g., human genome.

- Use `CEq-EA` to prepare a `MIG` specification to fit the reality of the specified systems. The specification consists of influences that have appropriate semantics after making arguments on the real biological interactions.

- Discover for emergence behind the complex of biological interactions. The treatment of multiple equilibria may lead to identify emergent properties under homeostasis.

In technically, we will refine the use of parameters in the whole method, and also explore for appropriate analytic parameters: modalities, object attributes, parameters for sanitation. Beside that, we are going to provide a friendly-user interface; e.g., direct input with influence graph.

5 List of Publications and/or Developed Systems

- J. Senachak, M. Vestergaard, and R. Vestergaard, Cascaded Games. The Second International Conference on Algebraic Biology (AB2007), *AB-2, LNCS 4545*, 2007. pp. 185–201.

- J. Senachak and R. Vestergaard, The CEq Emergence Assistant. (in preparation)
`http://cascade.jaist.ac.jp`

- R. Vestergaard, J. Senachak, and M. Vestergaard, Lamboid Emergence. JAIST Research Report: IS-RR-2008-001.