

Chemical Reaction Networks: Filipino Contributions to Their Theory and Its Applications

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This paper reviews the theory of chemical reaction networks and the contributions of Filipino scientists to it. The modern theory of chemical reaction networks began in the early 1970's with the work of American chemical engineers and chemists from Canada and Russia. The field was reshaped at the turn of the century with the emergence of systems biology and biologists, computer scientists, mathematicians, and researchers from other disciplines joining the collaborative efforts. Luis F. Razon, a chemical engineer, and Baltazar D. Aguda, a chemist, were the first Filipinos to contribute to the theory with their Ph.D. theses in 1985 and 1986, respectively. Over twenty-five years later in 2014, mathematicians from several Philippine universities revived the research – focusing on power law kinetic systems and biological applications – and contributing nine international publications since. The paper concludes with a description of their current research and some promising perspectives.

Keywords: chemical reaction networks, Filipino, history, theory

In Memoriam: Baltazar D. Aguda (1956–2017)

With his Ph.D. thesis in 1986, Baltazar “Baltz” D. Aguda became one of the first two Filipinos to contribute to the theory of chemical reaction networks (CRNT for short). Through his papers on the mammalian cell cycle in 1999, Baltz became the first scientist worldwide to apply CRNT to the emerging field of systems biology.

After an absence of more than 35 years, Baltz returned to the Philippines in May 2016 to become the Executive Director of the Philippine Genome Center and a Research Professor at the University of the Philippines. In August 2017, he succumbed to lung cancer – a tragic loss for the

country's research community. We dedicate this essay to the memory of this remarkable Filipino scientist.

Chemical reaction networks are collections of interdependent chemical reactions. Each reaction is represented as an ordered pair of vectors (called complexes) of chemical species and depicted as a directed arrow from the reactant complex to the product complex. The interdependence of the reactions results in the description of the network as a directed graph (or digraph). Each reaction is assigned a kinetic function – the product of a positive number (called the rate constant) denoting its assumed constant speed and a non-negative function of the concentrations of the chemical species specifying its interaction with other reactions. The kinetic function is

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typically chosen to be differentiable so that the dynamics of the chemical kinetic system is described by a system of ordinary differential equations (ODEs). The mathematical theory of chemical reaction networks and their kinetics, or CRNT as it is usually called, thus combines concepts and methods from the theory of digraphs, of vectors and matrices (linear algebra), and of dynamical systems (systems described by ODEs).

The Historical Development of the Mathematical Theory of Chemical Reaction Networks

An article in Wikipedia states that the mathematical discipline “Chemical Reaction Network Theory” was originated by Rutherford Aris, a famous expert in chemical engineering, with the support of Clifford Truesdell, the founder and editor-in-chief of the journal *Archive for Rational Mechanics and Analysis*. Indeed, Aris' two Prolegomena papers (1965 and 1968) led to a series of papers by other authors in the *Archive* journal, including a 1970 paper by F. Krambeck from which the important concept of a network's deficiency was developed in 1972 by Horn and Feinberg (1977). James Wei is also mentioned as a pioneer of CRNT in Feinberg (1977). These results contributed to form the basis of research of American chemical engineers in the 1970's, which in Section 2.2 we will refer to as “deficiency-oriented theory.”

We point out, however, in Section 2.3 that works by Canadian and Russian chemists in the same period built a second pillar of CRNT. The questions addressed and the methods developed by these researchers complemented those in the “deficiency-oriented theory” school. Our study in fact shows that researchers from this group have more readily established the connection of CRNT to the emergence of the field of systems biology.

In Section 2.4, we document how systems biology revived and reshaped CRNT, resulting in tremendous growth in terms of researchers involved and papers published in the last two decades.

The First Century of the Theory (1865–1971)

The roots of the theory of chemical reaction networks and kinetic systems go back to the studies of the Norwegian chemist Cato Maximilian Guldberg and mathematician Peter Waage (1879) on the Law of Mass Action between 1864 and 1879. The principle they established states that the rate of a chemical reaction is directly proportional to the product of the activities or concentrations of the reactants. Two important lines of development followed at the turn of the century twenty years later. The first centered on “detailed balanced systems” and was initiated by the German chemist Rudolf Wegscheider, who applied the principle of detailed balancing (also termed

“microreversibility”) to chemical reactions in 1901. This principle is valid for physico-chemical systems that are decomposable into elementary processes and entails that, at equilibrium, each elementary process must equilibrate with its reverse process.

The Austrian physicist Ludwig Boltzmann applied it in 1872 to collisions. Wegscheider's (1901) key result was the discovery of necessary and sufficient conditions for detailed balancing in mass action systems. In 1931, Lars Onsager – a Danish chemist – used the Wegscheider conditions to derive reciprocal relations that are basic for irreversible thermodynamics (the “Onsager reciprocal relations”), for which he was awarded the Nobel Prize in Chemistry in 1968. One of the pillars of CRNT, deficiency-oriented theory, directly extends the theory of detailed balanced systems.

The second important development in the theory of chemical reaction networks in this period was in the field of enzyme kinetics. It started also at the turn of the century with the work of the Frenchman Victor Henri in 1902, was continued by the English scientist Adrian Brown in the following years, and eventually completed by the German-Canadian duo Leonor Michaelis and Maud Menten in 1913. In 1925, G. E. Briggs and J. S. B. Haldane introduced the steady state concept to enzyme kinetics and further formed the Michaelis-Menten model as it is taught today.

Until the early 1950's, in contrast to the tremendous advances in experimental enzymology, kinetic studies remained based on the mid-1920's framework of unreactant enzymes. This changed in the mid-1950's, and the following table – which is based on Chapter 1, Section A of the book *Enzyme Kinetics* by Segel (1975) – summarizes the rapid progress in the following decade.

In contrast to detailed balanced systems, enzyme kinetic systems have received much less attention in the CRNT community according to Gabor *et al.* (2015) and Mincheva (2012), and remain a promising opportunity for research.

The Rise of Deficiency-oriented Theory (1972 Onwards)

The paper “*General Mass Action Kinetics*” by Fritz Horn and Roy Jackson (1972) was an early major highlight of CRNT. In that paper, they introduced the concept of a complex balanced system as a generalization of the hitherto more familiar detailed balanced systems of Wegscheider and successors. A system is complex-balanced at a state (*i.e.*, a species composition) if for each complex, formation and degradation are at equilibrium. They showed that complex balanced systems form a subset of quasi-thermodynamic systems, a concept introduced by D. Shear in 1968, who also proved the uniqueness in

Table 1. Progress in enzyme kinetics in the mid-1950's.

Time Period	Methods/Results	Comments
mid-1950's	First Michaelis-Menten-style rapid equilibrium-based attempts for bi- and terreactants	Formally easy, but often disagreed with enzyme behavior
late-1950's	Steady-state based approaches (<i>e.g.</i> , Dalziel, Alberty, Hearon)	Equations too complex and not expressed in familiar K_m , K_i , and V_{max}
1963	Uniform procedure for writing kinetic equations for multireactant steady state enzyme systems (Cleland)	Also had a convenient shorthand nomenclature for describing mechanisms
1965	Kinetic model for allosteric enzymes (<i>i.e.</i> , regulatory enzymes which displayed sigmoidal curves (Monod, Wyman, and Changeux)	Usual velocity curves are hyperbolic and not sigmoidal
1966	Alternate allosteric model (Koshland, Nemethys, and Filmer)	Based on Koshland's flexible enzyme induced fit model (1959)

each stoichiometric compatibility class of their equilibria. However, this uniqueness result is nowadays called Birch's Theorem, since a mathematically equivalent result to Horn and Jackson's was derived already by Birch (1963) in a paper in algebraic statistics. Building on these studies, at a conference two years later, Horn proposed the global stability of the equilibrium, which today is called the "Global Attractor Conjecture" (GAC) and was proven only in special cases until January 2015 when G. Craciun announced a general proof. The proof has been exposed to extensive public peer review and is currently being prepared for final publication.

A subsequent paper by F. Horn (1972) was just as important for CRNT as it – together with a back-to-back paper of Martin Feinberg (1972) – introduced the concept of network deficiency. This non-negative integer measures the degree of linear dependency of the reactions in the network. Feinberg's definition, which later became the standard, is particularly intriguing as it involves a combinatorial value – a topological invariant and the dimension of a linear subspace. These papers also derived the first significant connection between network structure and chemical kinetics, which we call the Core Deficiency Zero Theorem. Mass action kinetic systems are complex balanced for every rate vector if and only if the underlying network is weakly reversible (*i.e.*, each reaction lies in a directed cycle) and has deficiency zero.

The Deficiency Zero Theorem (DZT) for mass action kinetic systems, in its current form, was first stated in a joint paper by Horn and Feinberg (1974). A sketch of the proof was provided three years later in a book chapter by M. Feinberg (1977), and a full proof can be found in his University of Wisconsin lectures (1979). While the DZT is correctly attributed jointly to F. Horn, R. Jackson, and M. Feinberg, it should be clear from the previous discussion that the major contribution was from F. Horn. M. Feinberg's (1979) lectures are still a rich source for CRNT, especially because it provides a very clear presentation of a fundamental result about the kernel of a k-Laplacian

mapping, which we call the Structure Theorem of the k-Laplacian Kernel. A key feature is the purely structural approach independent of particular kinetic considerations. The largely forgotten equivalence of weak reversibility with what we term "complex balancing" is also clearly shown in these lecture notes.

A further joint paper by Feinberg and Horn (1977) studied the relationship between the stoichiometric subspace of a CRN and its subset – the kinetic space – which is the smallest linear space containing the image of the species formation rate function (SFRF) for mass action kinetics (MAK). They established the importance of the topological "terminality" – the difference between the number of terminal strong connected components and the number of connected components of the network – for determining whether the kinetic subspace coincides with the stoichiometric subspace or not.

It is impressive to see that already in these papers in the 1970's, the pioneers of CRNT – Horn, Jackson, and Feinberg – already foresaw future important themes/developments in the field. In their 1974 essay, Horn and Feinberg emphasized the importance of the biochemical studies of complex isothermal open systems leading to sustained periodic behavior (biological clocks) and bistability – an anticipation of the systems biology-based upsurge of CRNT research in the first decade of the 21st century. The earliest papers of Horn with Jackson (1972) and Feinberg (1972) were concerned with kinetics more general than MAK – studies of such kinetics are emerging as an important trend in today's research. Another such contemporary development, the consideration of non-chemical networks, was already within their sight, too – as Horn and Feinberg stressed in their 1974 essay and underscored by the frequent use of the Lotka-Volterra system from ecology as an example in their work.

Extensions of deficiency-oriented theory to MAK systems on networks of positive deficiency constituted the main results of CRNT in the following two decades. This

work was carried out solely by Feinberg and his students and consisted of three main results: the Deficiency One Theorem (DOT), the Deficiency One Algorithm (DOA), and the Advanced Deficiency Algorithm (ADA). In a 1987 review, Feinberg also formulated the "Persistence Conjecture" *i.e.*, that every MAK system on a weakly reversible network is persistent, essentially an extension of the GAC to networks of higher deficiency and still wide open.

The DOT is stated for the first time in Lecture 3 (Theorem 3.2) of Feinberg's (1979) lectures for the weakly reversible case and a proof was announced for Lecture 7 (which is no longer available). A year later, Feinberg stated the theorem in a book chapter and listed an upcoming paper with its proof in the references. However, it took another 15 years before a lengthy, complete proof was published by Feinberg (1995a) for a more general formulation for the superset of t-minimal networks (t-minimal means that each connected component is a terminal strong component) and the network deficiency is the sum of the component deficiencies – each of which is less than or equal to 1.

Since there are many networks of deficiency one and higher not covered by the DOT, Feinberg developed the DOA to handle them. The DOA was first discussed in the second of two reviews published by Feinberg (1987 and 1989). The algorithm and the mathematical theorems underlying its validity were published in a companion paper to the DOT paper also by Feinberg (1995b). Version 1.0 of the Chemical Reaction Network Toolbox (a DOS program) made the DOA available for use by other researchers.

The ADA was developed by Feinberg's student, Phillip Ellison (1998), in his Ph.D. thesis at Ohio State University. It extends the DOA to handle networks with deficiency greater than 1. ADA was made available to the user community through the CRNToolbox V1.1.

Two further contributions by Feinberg and his students during this time should be mentioned: Feinberg (1989) contributed a clarification to the necessary and sufficient conditions for detailed balancing with his structuring of these into "cycle conditions" and "spanning tree conditions." This was very useful for the chemical community, as it also showed the relationship to concurrent work by S. Schuster and R. Schuster (1989) on generalized Wegscheider conditions. The other contribution was the development of new graphical approaches, initially with the Ph.D. thesis work of Paul Schlosser (1994) with M. Feinberg on Species-Complex Linkage graphs.

The Emergence of Stoichiometric Network Analysis (1973 Onwards)

Bruce Clarke's work on Stoichiometric Network Analysis (SNA) began in 1973 with his graphical studies of

chemical systems, such as the bromate-ceriummalonic acid (the basis of the then famed Belousov-Zhabotinski reaction). He was interested in analyzing under which conditions chemical systems had the potential to display oscillations, with his seminal papers (1975a and 1975b). A comprehensive description of the SNA framework and methods appeared in Clarke's (1980) book chapter. Domijan and Kirkilionis (2008) provide the following succinct assessment of Clarke's work, where they generalize some of his main results:

"The crux of Clarke's idea was to observe the dynamics of the system in reaction rate space, rather than in the species concentration space. This was revolutionary because it significantly simplified model analysis. Instead of searching for steady states where all concentrations are unknown and parameters are not specified, their analysis was restricted only to dealing with reaction rates. Clarke and his collaborators extended this idea where they derived several conditions on the reaction rates. By assuming the existence of a positive concentration steady state, its linearization will have either a zero eigenvalue or a pair of purely imaginary eigenvalues. These eigenvalue conditions will then form a necessary condition for the positive concentration steady state to be a saddle point or a Hopf bifurcation point."

As a foundation for these studies, Clarke (1981) – beginning with his analysis of the Belousov-Zhabotinski oscillatory system – also pioneered the use of convex analysis to probe the structure of the cone formed by the intersection of the kernel of the stoichiometric map/matrix and the set of positive vectors in reaction space. Minkowski's Theorem then provided a unique set of convex generators for the cone, which Clarke termed "extreme currents." This work – often not given the proper credit – also laid the foundations for the reconstruction of genome-scale metabolic networks in the decade to follow. Clarke and his co-authors never confirmed the existence of the positive concentration steady state they assumed. This gap was filled much later by the work of Karin Gatermann (2002) and collaborators in the early 2000's, which used sophisticated tools from algebraic geometry.

Further contributions to SNA came from a Russian researcher, A.N. Ivanova (1979), in several papers. Mincheva and Roussel (2007), who did the CRN community an important service in 2007 by recounting Ivanova's work and filling up some gaps in the derivation, wrote:

"In Ivanova's version of SNA, a chemical mechanism is represented by a bipartite graph of chemical species and of reactions. Bifurcations leading to oscillations or multistability (collectively referred to as "instabilities") in the differential equation model occur when one of the coefficients of the characteristic polynomial of the

corresponding Jacobian changes sign. This requires a negative term in the coefficient, since the majority of the terms are positive. Nonzero terms in the coefficients of the characteristic polynomial correspond to subgraphs of the bipartite graph. Finding the subgraphs corresponding to the negative terms thus identifies subnetworks responsible for instabilities."

Baltazar D. Aguda and Luis F. Razon: Filipino Pioneers in the Theory of Chemical Reaction Networks

Baltazar D. Aguda (1956–2017)

Table 2. Education of Dr. Baltazar D. Aguda.

Years	Institution
1974–1978	University of the Philippines Los Baños (UPLB) B.S. Agricultural Chemistry, <i>cum laude</i> NSDB Scholar
1980–1982	University of Alberta, Canada M.S. Chemistry
1983–1986	University of Alberta, Canada Ph.D. Chemistry



After finishing his B.S. in Agricultural Chemistry degree at UPLB, Baltz Aguda began his graduate studies at the University of Alberta (Canada), finishing his M.S. in Chemistry in 1982. Baltz received a dissertation fellowship and completed, as the first Ph.D. student of Bruce Clarke, his thesis entitled "*The geometry of steady states of chemical reaction networks*" in 1986 –

marking the first Filipino contribution to CRNT.

Baltz continued his research on chemical reaction networks using the SNA approach in a series of postdoctoral positions between 1987 and 1993 at Indiana University (USA) and the Universities of Waterloo and York in Canada. During this period, he published 11 papers (cf. Appendix 1) analyzing complex system behaviors such as multiple steady states, oscillations, and chaos – mainly in the *Journal of Chemical Physics*. Models of the aerobic oxidation of nicotinamide adenine dinucleotide catalyzed by the horseradish peroxidase enzyme – denoted as the *peroxidase-oxidase* reaction – constituted a focus of his research, with over half of his papers' titles mentioning the system.

A particularly interesting concept from the early papers of Aguda and Clarke (1988 and 1989) was that of a

"dynamic element" of a chemical reaction network. A dynamic element is a minimal subnetwork displaying a complex system behavior such as an oscillation. The concept, hence, attempts to map dynamic behavior to structural components of the network. In a related effort, Aguda and Clarke (1987) also attempted to formulate a general SNA-oriented procedure for determining multiple steady states in a chemical reaction network. After Bruce Clarke left academe in 1992, it was Baltz and collaborators who continued contributions to CRNT using the SNA approach.

The move in 1994 to a tenured position at the Department of Chemistry and Biochemistry of the Laurentian University (Canada) marked an important turning point in Baltz's career. Biological and biochemical systems became a focus of his work (1996), as initial publications in 1996 indicate. Understanding the complex oscillatory dynamics of the cell cycle – a particularly "hot topic" in biology in the 1990's with many of its molecular mechanisms were being revealed – emerged as his main research topic.

In 1999, Baltz Aguda (Aguda 1999a, b; Aguda and Tang 1999) published three papers modeling the mammalian cell cycle. They focused on the dynamics of the cycle's two crucial checkpoints: the restriction point between the G1 and S phases, and the DNA damage control point between the G2 and M (mitosis) phases. Though his models were not the first published on the topic, they have had the highest impact among the early ones – as the following account in a recent, comprehensive review by Abroudi *et al.* (2015) testifies:

"In 1999, Aguda and Tang published a detailed mathematical model to investigate the kinetic origin of restriction point in mammalian cell cycle. In the same year, Aguda (1999b) explored the effect of DNA damage on G2/M checkpoint. Iwamoto *et al.* (2008), who partly utilized Aguda's models, started to develop more complex models of mammalian cell cycle checkpoints and investigated the effect of DNA damage (following UV-irradiation) on G1/S transition in mammalian cell cycle. This study inspired Ling *et al.* (2010) to investigate the robustness of G1/S checkpoint in depth. Using Type II Error, they introduced a novel approach to quantify the percentage of damaged cells passing G1/S checkpoint under different system perturbations. In 2011, Iwamoto *et al.* added G2/M checkpoint to their previous model in order to make it more comprehensive and meaningful as it then covered almost the whole cell cycle. This model was insightful in that it could determine cell fate based on DNA damage strength."

Baltz's second 1999 paper (1999b) was also his first publication in the high-impact journal "Proceedings of

the National Academy of Science.”

These papers, together with a follow up review in 2001, were significant from a further perspective: they marked the first application of CRNT to systems biology. In Aguda’s (1999a) earliest 1999 paper, Baltz first listed the phosphorylation-dephosphorylation (PD) cascade structures capable of generating instabilities [Figure A *i.e.*, Figure 3 (1999a)]. He then identified which of the PD cascades occurred at the cell cycle checkpoint [Figure B *i.e.*, Figure 7 (1999a)]. He then derived the qualitative checkpoint (dynamic) behavior from their interactions [Figure C *i.e.*, Figure 8 (1999a)]. This is a clear example of what Bailey called “complex biology with no parameters.” In addition, in his second 1999 paper (1999b), he explicitly cited a 1974 paper by Feinberg and Horn to explain and justify his analysis approach:

“In the mathematical field of reaction network analysis,

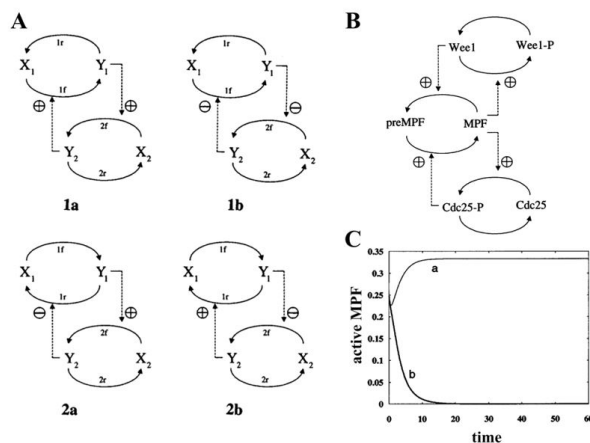


Figure 1. Phosphorylation-dephosphorylation cascades figures lifted with permission from (Aguda 1999a). The (+) symbol indicates that species Y_i catalyzes the reaction, while (U) means inhibition.

some promising results show that just knowing the structure of the network is sufficient to deduce certain possible behavior of a network independent of the values of the rate parameters; see for example the work of Feinberg and Horn (1974).”

Baltz Aguda was not only the first Filipino to contribute to CRNT and the first scientist to apply CRNT to systems biology. He became an active member of the North American community of scientists that contributed to the emergence of systems biology at the turn of the century. During his sabbatical at Caltech in 2001, he helped kick-start the team of computer scientists and control engineers in their effort to build a standard language for modeling biological systems by, as he once joked, teaching them

“chemistry.” Seventeen years after these “lessons” from Baltz, SBML has indeed become the global standard in the field.

Baltz continued his stellar career in systems biology at several institutions, including the new Mathematical Biosciences Institute (MBI) at Ohio State University. He was a close collaborator of its Founding Director, the renowned mathematician Avner Friedman, with whom he co-authored a book “Models of Cellular Regulation” (Oxford University Press 2008). They also published a joint paper on a model of the cell cycle and apoptosis in 2005 with Gheorghe Craciun, then a postdoc fellow at MBI and now one of the leading researchers in CRNT. Baltz’s significant contributions to systems biology between 2001 and 2017 are too numerous to list here and should be the subject of a separate essay. To date, however, this pioneering achievement of Baltz Aguda remains unrecognized in the CRNT community. We hope that our essay will contribute to make this significant Filipino contribution better known in the scientific world.

Luis F. Razon (1958–)

Table 3. Education of Dr. Luis F. Razon.

Years	Institution
1975–1980	De La Salle University B.S. Chemical Engineering, <i>magna cum laude</i> Insular Life Educational Foundation Scholar
1980–1981	University of Notre Dame, USA M.S. Chemical Engineering
1981–1985	University of Notre Dame, USA Ph.D. Chemical Engineering
1985–1986	University of Notre Dame, USA Post-doctoral studies



Luis “Louie” F. Razon went to De La Salle University (DLSU) for his Bachelor’s degree in Chemical Engineering. Following the advice of his mentor, Dr. King Co, Louie pursued graduate studies at the University of Notre Dame in USA. Louie stayed there for six years. Within those six years, he finished his Master’s degree in a year, Doctorate degree in 3.5 years, and Post-doctorate in 1.5 years. Afterwards, he returned to DLSU, taught for a year and a half, then ventured into industry. After working in

industry for almost 12 years, Louie went back to DLSU to resume teaching and conducting research.

In the beginning of Louie's graduate studies, he wanted to work on catalysis and thought that he would be developing catalysts for his thesis. However, this changed when he listened to Roger Schmitz's professorial chair talk on oscillation and multi-steady states. Attracted to Schmitz's research on Dynamical Systems, he worked with Schmitz on the dynamical behavior of catalytic systems. Razon completed his thesis, "*Intrinsically Unstable Behavior during the Oxidation of Carbon Monoxide on Platinum (oscillations, chaos, catalyst)*," in 1985. He was the second graduate student of Schmitz at Notre Dame.

Louie's work with Schmitz was the first to demonstrate chaos in a heterogeneous catalytic system. During this time, Louie also learned how to acquire data by connecting instruments to the computer, a crucial step for documenting and analyzing whether the system was chaotic or not. Initially, their goal was only to see the existence of oscillatory behavior of the single cycle reactant but, interestingly, they were also able to observe the chaotic behavior of the said system. Excited about their findings, they were able to recreate the strange attractor from their time-series data and show that the dimension is fractal. This led to the 1986 paper, Louie's first on CRNT, entitled "*Chaos during the oxidation of carbon monoxide on platinum—Experiments and analysis.*" This paper would earn 55 citations. The techniques used in the study were novel, and with it they were able to arrive at a firm conclusion that the system was indeed chaotic and not stochastic.

Louie and Schmitz would publish their two most cited papers in 1986 and 1987. The paper, "*Intrinsically unstable behavior during the oxidation of carbon monoxide on platinum*" by Razon and Schmitz (1986a), has been cited 266 times to date. The 1987 review article "*Multiplicities and instabilities in chemically reacting systems*" has recorded 212 citations so far. These papers are considered classics in the area of dynamical systems applied to chemical reactors.

Louie continued his work on dynamical systems and produced five other related publications on dynamical analysis and chaos (Schmitz *et al.* 1984a, b; Lai *et al.* 1994; Razon 2005, 2006). In 2005, when he returned to the academe, Louie tried to extend the "classic" continuous stirred tank reactor model by adding the reactor heat capacity (Razon 2005, 2006), hoping that it would lead to chaotic behavior. Instead, they arrived at stable steady states. He observed a sharp reduction in the oscillatory region yet, contrary to his hopes, there was no chaotic behavior. In 2007, due to limited funding opportunities in the nature of his research work, Louie decided to shift

his research directions to biodiesel production and life cycle assessment. Ten years later, in January of 2017, his interest in dynamical systems and chemical reaction network theory was revived.

Systems Biology Revives and Reshapes Chemical Reaction Network Theory (2000 Onwards)

The Rise of Systems Biology

Systems biology has rapidly emerged as one of the leading paradigms for the life sciences in the early 21st century. The year 2000 was significant for the field's emergence not only because of the completion of the Human Genome Project, but also due to three pioneering efforts: the founding of the Institute for Systems Biology in Seattle (headed by Leroy Hood), the occurrence of the First International Conference on Systems Biology in Tokyo (chaired by Hiroaki Kitano), and the initiation of activities for SBML (Systems Biology Mark-up Language) mainly led by John Doyle at Caltech. The integrative approach has captured the imagination of biologists and the wider scientific community. Its growing influence has led to the establishment or re-focus of many research groups and institutes, including Harvard Medical School's establishment of a Department of Systems Biology – its first entirely new one in 20 years – with a substantial investment in resources and facilities. By 2004, Ph.D. study programs in systems biology were established, led by the three top US universities – MIT, Harvard, and Princeton. A plethora of new scientific events and journals with "systems biology" in their titles emerged, and established ones added significant subsections devoted to the field. National and international initiatives for systems biology, coupled with the provision of substantial funding, have been launched worldwide.

Though Baltz Aguda's papers pioneered the application of CRNT in systems biology, it was J. Bailey's essay "Complex biology with no parameters" in the June 2001 issue of Nature Biotechnology that highlighted the potential of qualitative analysis and modelling for systems biology for a wider scientific audience. He listed the work of Horn, Jackson, and Feinberg (*i.e.*, deficiency-oriented theory) as one of the most promising approaches and discussed structural aspects of SNA (in the context of flux balanced analysis). Examples of applications of CRNT to biological problems followed soon – the first published after Aguda's papers being the work of E. Sontag's (2001) group on T-cell proofreading. The online availability of Feinberg's 1979 lectures – J. Gunawardena's 2003 Harvard lecture notes "Lectures on Chemical Reaction Network Theory for in-silico biologists" and more advanced versions of the CRNToolbox – accelerated the spread and scope of these application activities.

An important new development was the theory of injective kinetic systems, which G. Craciun and M. Feinberg established in a series of papers between 2005 and 2010. Injectivity is a sufficient condition for monostationarity, and the Jacobian determinant criterion they derived proved to be a useful (and extensible) computational tool for its verification. The research on injective systems also contributed to the renewed interest in graph-theoretic methods with the introduction of the species-reaction graph. Connections with earlier constructs by A.N. Ivanova and the vast theory of Petri nets were established, particularly by E. Sontag's group (2001). The resolution of some long-standing conjecture of R. Thomas (1981) on interaction graphs by C. Soule (2003) and collaborators also marked significant achievements in graph-theoretic approaches to CRNs in this period.



G. Craciun and his students also contributed fundamental results on the identifiability of CRNs *i.e.*, criteria for different CRNs to generate the same ODE system, which were later developed into what has been termed "Realization Theory" by Hungarian and Canadian researchers – with methods based on linear and mixed-integer programming. Another

paper from the Craciun group pioneered the use of homotopy theory for counting steady states, which became the basis a few years later for results of Joshi and Shiu (2013) on "lifting" equilibria from subnetworks to the encompassing networks.

On the SNA side, K. Gatermann and collaborators in Berlin and Magdeburg, Germany, closed a crucial gap in the theory – establishing a stringent relationship between equilibria in reaction coordinates to the (usual) ones in concentration space. This involved the deep use of algebraic geometry. These research groups also developed novel methods of inferring multistationarity from subnetworks to the parent network. Another SNA-based development – though often not acknowledged as such – was the extensive use of convex analysis approaches. It is in the form of "extreme pathways" or "elementary flux modes" in the genome-wide reconstruction of cellular networks, in particular metabolic networks of microorganisms. This became feasible through the availability of "omics" data generated by new high-throughput methods. The group of L. Kolar-Anic in Belgrade (Serbia) improved various SNA methods and demonstrated their application to different chemical and biochemical systems.

The First Decade of Systems Biology in the Philippines (2003–2013)

Activities in systems biology in the Philippines were introduced by an initiative of Ed Mendoza, who conducted graduate courses in "Mathematical and Computational Modeling of Biological Systems" at UP Diliman (UPD) and De La Salle University starting in January 2003. With the support of Ric del Rosario (then Chairman of the UPD Department of Mathematics), he also organized collaborations between experimental scientists and modelers, which later evolved into the interdisciplinary SMILES (Statistics, Mathematics, and Informatics in the Life and Environmental Sciences) initiative.

The collaboration with the Concepcion Lab at the UPD Marine Sciences Institute on apoptosis induction in tumor cells by marine natural products was particularly successful, resulting in the completion of one Ph.D. and three M.S. theses plus two international publications.

However, it soon became clear that only a few experimental groups in the Philippines had the kind of data needed for systems biology approaches. The SMILES research community developed two complementary strategies to address this problem: first, it focused primarily on computational approaches; and second, explored collaborations with experimental groups abroad, primarily in Europe. The second alternative had become feasible with the availability of Internet tools such as Skype and met the needs of the experimental groups, which lacked computational expertise.

On the computational side, the Filipino researchers focused on modeling methods from biochemical systems theory (BST), which consistently applied power law differential equations. The group achieved novel contributions for parameter estimation, as well as comparative analysis of power law systems. In particular, the use of nature-inspired stochastic algorithms such as simulated annealing or particle swarm optimization caught the attention of the international BST community, which led to productive collaborations. Highlights of the BST research between 2003 and 2013 were ICMSB 2008, the 10th bi-annual BST meeting that took place at UP Diliman (25–28 Feb), and 12 international publications in the period. Concepts on power law systems, BST, and the like can be found in an openly accessible review by E. Voit (2013).

On the experimental side, significant collaborations included those with the Oesterheld Lab at the Max Planck Institute of Biochemistry, and the Raedler Lab at the Ludwig Maximilians University (LMU) – both in Munich, Germany. The work with the Oesterheld Lab (2010) centered on the systems biology of halophilic archaea and, supported by three Ph.D. scholarships and two postdoctoral fellowships (sponsored by the Max

Planck Society), resulted in nine joint publications. The LMU collaboration was focused on modeling the uptake of nanoparticles in human cells (Dobay *et al.* 2013). Novel methods based on stochastic process algebra were developed, with a Ph.D. scholarship and two post-doctoral fellowships supported plus six publications achieved.

The Revival of Filipino Contributions to the Theory of Chemical Reaction Networks (2013–present)

The paper entitled “*The role of theorem proving in systems biology*” of Wolkenhauer *et al.* (2012) – highlighting the achievements of CRNT, including a recent paper by Shinar and Feinberg (2010) on absolute concentration robustness in the high-impact journal *Science* – pointed the Filipino researchers to a third alternative. After studying CRNT literature over several months, E. Mendoza became convinced that the field promised interesting research for the mathematicians in the research community. The discovery that Baltz Aguda was an early contributor to the field provided additional motivation to engage in it. The application to modeling signaling networks of the renal dopamine system and of plant hormones in several MS Math theses co-advised by C. Arceo and E. Jose at UP Diliman and UP Los Baños, respectively, constituted the initial research efforts. These results were reported at the 2nd Asian Regional Conference in Systems Biology at Kuala Lumpur in October 2013. A further fortuitous event was the publication of a paper of L. Cardelli on morphisms between mass action systems in early-2014. These results were extended partially by E. Mendoza to power law kinetic systems and this success gave birth to the idea of a two-pronged research program of: i) extending MAK results to power law kinetic systems; and ii) connecting BST to CRNT and, thus, providing the latter with many interesting complex biological systems as case studies. This also encouraged E. Mendoza to start a graduate course on the “Mathematics of Chemical Reaction Networks and Kinetic Systems” (MCRNKS) at UP Diliman in August 2014. A research workshop in September 2014 launched the group’s thrust toward international publications.

The Filipino researchers succeeded in publishing a first paper (Arceo *et al.* 2015) almost exactly a year later (published online September 2015 in *Mathematical Biosciences*). Primarily addressing the BST research community, they contributed formal CRN representations of GMA and S-systems and analyzed their fundamental properties. The paper identified the important subset PL-RDK of power law systems with reactant-determined kinetics (those with equal kinetic order rows), which contain the MAK systems and essentially correspond to the General Mass Action Kinetics systems of Müller and Regensburger (2014).

Further novel results were the discovery that the BST model of human purine metabolism (Curto *et al.* 1998) was not PL-RDK, complex factorizable systems as a generalization of PL-RDK and the partial extension of Cardelli’s results mentioned earlier. A substantial part of the paper discussed CRNT results applicable to the analysis of BST models.

Their second paper (Arceo *et al.* 2017, published online Nov 2016 in the same journal), on the other hand, presented novel properties of the 27 CRNs derived from 15 BST case studies as well as new results abstracted from them – including the algebraic properties of many kinetics sets and the role of the branching type of a CRN for the availability of kinetics sets. The new concept of span surjectivity of a map between finite-dimensional vector spaces allowed the identification of the key subset of factor span surjective kinetics and enabled the generalization of the Feinberg-Horn Subspace Coincidence Theorem for MAK systems (1977) to complex factorizable systems. The generalization includes an improvement from M. Feinberg, which resulted from an exchange of emails with E. Mendoza, during which the former also revealed that he was the main reviewer of the first paper.

The remaining five publications of the group and their students focused on extensions of interesting results on MAK systems. Two extensions turned out to be surprisingly straightforward: Cortez *et al.* (2018) showed that the Johnston-Siegel criterion for linear conjugacy and the MILP algorithms based on it were valid for power law kinetics with reactant-determined interactions. Fortun *et al.* (2018a) derived Feinberg’s DOA for the same set of power law systems.

The other three papers on the other hand opened new areas of research in CRNT: Talabis *et al.* (2018) identified a subset of power law kinetics for which analogues of the Low Deficiency Theorems for MAK systems were valid. Arceo *et al.* (2018) developed a systematic theory of the reactant subspace of a CRN and showed new connections to the network’s kinetics. A surprising connection between both papers was observed for a subset of MAK systems. Mendoza *et al.* (2018) extended the results of Talabis *et al.* to weakly reversible systems of higher deficiency. Two of the five papers were based on thesis work: the M.S. thesis of D. Talabis and the Ph.D. thesis of N. Fortun. Two further papers by Fortun *et al.* are in press.

The papers of the Filipino contributors are all listed in Appendix A.

CRNT – A Mathematical Discipline With Tradition and Promise for Filipino Researchers

The initial publication successes and further graduate

courses at UP Los Baños and De La Salle University have led to the formation of an active research community consisting of around ten senior researchers and five Ph.D. students. The group has begun to present their results at local scientific meetings, including the annual congress of the Mathematical Society of the Philippines. Contacts with the international CRNT community have led to the invitation of A. Lao to present at a CRNT symposium in the SIAM Conference on Applied Algebraic Geometry at Georgia Tech in August 2017, a research visit by C. Pantea in December 2017, and the participation of E. Jose and A. Lao at a CRNT mini-symposium at the annual meeting of the Society for Mathematical Biology at the University of Sydney in July 2018. At the first International Workshop of Mathematical Biology (IWOMB) in Cebu City in January 2018, E. Mendoza did a presentation on the pioneering work of B. Aguda in applying CRNT to Systems Biology.

Current research areas in the group, including those of the Ph.D. theses, are focused on power law kinetic systems. Initial extensions to the main focus of chemical network research, the set of all kinetic systems with constant reaction rates, have been found. Furthermore, initial exploration of new areas for applications, such as climate engineering and evolutionary games, has been successfully carried out. The personal involvement of our pioneer, Louie Razon, in these research efforts is certainly a striking example of Filipino “*bayanihan*” (Engl: cooperative endeavor) across generations of researchers.

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