

## Systems nutrition: an innovation of a scientific system in animal nutrition

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## 1. ABSTRACT

The traditional scientific system of animal nutrition has existed for over 100 years, but substantial changes are yet to take place. With the lapse of time, limitations of this traditional scientific system have been more and more evident and such a system should be dramatically revised with innovations. Beginning in the late 1980s, our group started to use system-science principles and approaches in animal nutrition research. The author published a book entitled “An Introduction to Systems-Nutrition of Animals”, which marked the birth of a new scientific system in animal nutrition to stimulate further development of this discipline. System-nutrition is defined as a branch of biological sciences that concerns system-level studies of the integrative picture of flux, metabolism, utilization and regulation of nutrients (e.g., proteins and amino acids) from dietary and endogenous origin in the whole animal system at organism, organs, tissues, cells and molecules levels to achieve such goals as nutritional manipulation and prediction, as well as optimum feeding decision and optimum nutritional engineering programs for animal feeding.

## 2. INTRODUCTION

Since the traditional scientific system of animal nutrition was proposed more than 100 years ago, there have not been substantial changes in either theory or practice of livestock and poultry feeding. With the lapse of time, limitations of the traditional scientific system have been more and more evident. Examples are that: a) nutritionists are still not used to think outside the box; b) animal weight gain or production performance is the only criterion for outcome assessment; c) the scope of studies are only at whole-body and digestive levels although nutrition studies at microcosmic levels have been started just recently; d) static description is still the major feature in nutrition studies; e) reduction and black box methods are the characteristics of the discipline. The times are calling for innovations to dramatically change the traditional scientific system. In recent years, two attempts have been made to this effect: a) the systems nutrition concept of De-Xun Lu (1) in 2004 as a new mode of thinking in animal nutrition; and b) establishment of decision goals for animal feeding proposed by C.A. Adams in 2001 (2). The major objective of this article is to highlight the advances in systems-

nutrition as a new scientific system in animal nutrition and feeding.

### 3. HISTORICAL BACKGROUND

All scientific systems must be based on a specific mode of thinking, and no exceptions can be made. In biological science, analytics-reductionism occupied the leading position of the mode of thinking for many years, but great progress in this field has been made during the past decade. Some disciplines have already completed the change of mode of thinking from analytics-reductionism to system approach, and changes in other disciplines are now in progress. In animal nutrition, a historical change of the mode of thinking is now underway and is expected to transform animal agriculture.

In the late 1980s, our group started to use system science principles and approaches in animal nutrition research. In August 1994, I was the first to propose the scientific term “systems-nutrition” in a meeting held in Inner Mongolian Agricultural University (3). Two years later, at the 7<sup>th</sup> National Conference of the Society of Animal Nutrition, Chinese Association of Animal Science and Veterinary Medicine, I summarized our progress that had been made between the late 1980s and 1996 in using system science principles and approaches in the animal nutrition field. In the August 2004, a book entitled “An Introduction to Systems-Nutrition of Animals” was published by me in China (1), which marked the birth of systems-nutrition of animals and the beginning of the period of further development of this discipline. Since then, much progress has been made, but we clearly recognize that there is still a long way to go. The first National Forum on Systems -Animal Nutrition Development was held in Yang Zhou University in 2008, after which four subsequent National Forums on this subject were held in 2009, 2010, 2011 and 2012. These conferences greatly promoted dissemination and development of System-Animal Nutrition in China. The convening of Session 4 “Advances in System-Animal Nutrition” at the American Society of Dairy Science-China joint conference on dairy Science and product quality (Beijing, China; May 11-13, 2013) fostered international cooperation in the development of Systems-Animal Nutrition.

### 4. A NEW SCIENTIFIC SYSTEM FOR ANIMAL NUTRITION

Systems-nutrition is defined as one of branches in biological sciences, which is engaged in system-level understanding of and in studying the integrative picture of flux, metabolism, utilization and regulation of nutrients (e.g., protein and amino acids) from dietary and endogenous origin in the whole animal nutritional system at whole-body, organs, tissues, cells, and molecules levels, to achieve some goals, such as nutritional manipulation and prediction as well as optimum feeding decision, and to organize the design and execution of nutritional engineering programs for animal feeding. Simply, systems-nutrition can be defined as an approach to studying animal nutrition using system science principles.

The major contribution of systems-nutrition is establishment of a new scientific system for animal nutrition, which has the following distinct features. First, systems-nutrition is entirely based on the mode of thinking driven by system science knowledge and is very different from the traditional scientific system. Second, a major object of study in systems-nutrition is the whole animal nutritional system, including organs, tissues, cells, and molecules, as well as the environment surrounding animals. Third, a goal of study for systems-nutrition is set at realizing nutritional manipulation as a mark of control science of this discipline. Forth, a systems-integrated type of technologies for research and application is the marked technologies for systems-nutrition. The new scientific system for animal nutrition consists of four parts.

#### 4.1. The animal nutritional system (including definition and analysis)

The animal nutritional system is a scientific term advanced by pioneers in the field, and is oriented to an object of study for systems-nutrition, which has great significance in the formation of systems-nutrition theory. The term is defined as an intact whole-body system consisting of organs, tissues, as well as their microcosmic levels in the animal body and the surrounding environment, which are all involved in animal nutritional processes. There are three basic functions in the animal nutritional system: a) fluxes, metabolism, and utilization of nutrients, as well as regulation of these processes; b) energy flux and transformation; and c) cell signaling transmission.

#### 4.2. Manipulation of the animal nutritional system

There are two kinds of manipulation or regulation in animal nutritional processes, i.e. self-regulation by animals and man-made manipulation. The theory of self-regulation by animals is one of important parts of systems-nutrition theory. The theory of man-made manipulation of the animal nutritional system is called a systems-integrated type of nutritional manipulation theory. This theory has distinct features that are based on the mobilization of functions of nutritional self-regulation by animals, and by means of integration of nutritional and non-nutritional techniques. The following manipulation goal can be achieved: namely a) fully utilizing nutritional potential in the animal body; b) improving animal health, performance, feed utilization, and animal product quality; and c) reducing pollution into the environments to a certain extent.

#### 4.3. Techniques for studying systems-nutrition of animals

The establishment and development of modern techniques provide a foundation for studying systems-nutrition of animals. In 2004, De-Xun Lu advanced a new technique system that was divided into two parts, i.e. for research purpose and for practical application (1). The research technique system consists of *in vivo* and *in vitro* techniques, as well as digital simulation (modeling) techniques. It is important that those techniques must be integrated as a whole and be complemented each other and overcome each weak point by the other's strong points. The technique system for practical application consists of four

**Table 1.** Comparison between microcosmic nutrition and molecular nutrition

	Microcosmic nutrition	Molecular nutrition
Mode of thinking	By system science and approaches	Not very clear
Scope of studies	At microcosmic levels i.e. cells and molecular levels	At the same levels, but mainly limited to the molecular level
Way of thinking for studies	Emphasizing knowledge integration at the microcosmic and other levels in the animal body horizontally and vertically	No emphasis on knowledge integration
Research methods	Using techniques of molecular biology and systems biology as well as of animal nutrition	Mainly using techniques of molecular biology

kinds of techniques, such as nutritional manipulation, monitoring nutritional status of animals, nutritional predication, and decision. Those techniques are successfully applied into the formation of integrated techniques system for animal nutrition engineering (4).

## 4.4. Integrated techniques for animal nutrition engineering

The details of this discussion will be given in the later part of this article. In essence, an optimized technique system for dietary formulation and nutritional management techniques are integrated according to well-controlled engineering methods in animal feeding. Additionally, monitoring techniques for the nutritional status are used as a tool to evaluate the integration extent, by which an integrated technique system for animal nutritional engineering is formed.

## 5. MICROCOSMIC NUTRITION STUDIES

With the rapid development of molecular biology and the technologies of gene engineering, various molecular biology technologies have been widely applied into nutrition research, leading to the birth of molecular nutrition in the 1980s. Since then, molecular nutrition has achieved great success worldwide. Studies of molecular nutrition would establish the basis to further interpret the mechanisms responsible for utilization of all nutrients at cellular and molecular levels in animals, which contribute to the development of animal systems-nutrition. The molecular level is only one of many levels in the animal nutritional system, and molecular nutrition is a new field in animal nutrition studies. Data from studies at cellular and molecular levels should be interpreted by keeping the whole animal system in mind. Thus, it is not scientific and even harmful for studies of molecular nutrition to be substituted for studies of animal nutrition at other levels in the animal nutritional system.

Microcosmic nutrition studies are an important component of systems-nutrition. Microcosmic nutrition is defined as an approach with which the mode of thinking by system science is developed to integrate knowledge obtained from studies at a level and between the levels, the mechanism responsible for the absorption, transport, metabolism, utilization of nutrients of endogenous and exogenous origin at cellular and molecular levels, in order to understand the functions and regulation of nutritional processes at the microcosmic levels. Microcosmic nutrition studies can find its roots in molecular nutrition. However, microcosmic nutrition and molecular nutrition have significant differences (Table 1).

The development of the various “omics” approaches have dramatically changed the scientific

techniques and approaches used in molecular biology and biochemistry, which resulted in the birth of systems-biology (5). Using “omics” techniques and approaches can provide a great deal of information on the status and functioning of the animal nutritional system under study both from effects caused by changes in gene expression and also by differences in feeding managements and diets. Therefore, those “omics” techniques and approaches should receive a wide application in microcosmic nutrition studies. The following subjects in microcosmic nutrition have priority in study: a) studies on dynamic changes, and operative and regulation mechanisms for absorption, transport, metabolism and utilization of nutrients at microcosmic levels; b) studies on network of endocrine regulation and signal transduction influencing absorption, transport, metabolism and utilization of nutrients at microcosmic levels; c) studies on effects of environmental changes on metabolism and utilization of nutrients at microcosmic levels; d) studies on various interactions involved in nutritional processes, including gene-gene, gene-nutrient, nutrient-nutrient, nutrient-regulator interactions, and their effects on health and performance of animals; e) studies on nutrimentabonomics, especially on dynamic changes, and operative and regulatory mechanisms for various metabolites under changing internal and outside environments; f) studies on knowledge integration of absorption, transport, metabolism and utilization of nutrients between microcosmic and other levels in an animal body. This last study subject is the most representative for microcosmic nutrition studies and it clearly differentiates microcosmic nutrition from molecular nutrition.

## 6. NUTRIENT BALANCE AT MULTIPLE LEVELS

Research on the theory of nutrient balance is an old subject in animal nutrition. Recently, scientists have recognized the significance of nutrient balance in an animal diet. Unfortunately, the current theory is incomplete and in a primitive development stage. There are three main concerns with the current nutrient balance theory because the theory is only limited to dietary intake levels but lacks: a) scientific and practical parameters; and b) scientific methods for evaluating nutrient balance. Development of modern theory of nutrient balance in animal nutrition is an urgent task for all of us. In view of the current status of nutritional sciences, our group has devoted ourselves to studying internal balances of a nutrient for many years and achieved the following results.

1. A new theoretical framework of nutrient balance was proposed, and the traditional theory of nutrient balance was expanded from dietary intake levels to all levels in an animal body. The new theoretical framework is called the

**Table 2.** A series of parameters for evaluating dietary nutrients balances for lactating cows

Stage of lactation	Early	Mid	Late
Days of lactation	14-100d	101-200d	201-300d
Average milk yield kg/d	40	30	20
Dry matter intake kg/d	24-26	21-23	11-12
Dry matter intake (mean %BW)	4	3.5	3
RDP/RUP	1.5-1.86	1.86-2.33	2.33-2.50
SP /RDP	0.42-0.51	0.38-0.5	0.33-0.5
lys/Met	3.0-3.2	3.0-3.2	3.0-3.2
ADF/NDF	0.62-0.63	0.61-0.63	0.60-0.67
NFC/NDF	1.0-1.24	1.0-1.16	0.91-1.1
Forage NDF/RDS	>1.1	>1.1	>1.1
Starch/NDF	1.1-1.18		
NFC/RDP	2.94-3.4	3.08-3.93	3.08-4
CP/NEL (g/Mcal)	103.7-115.9	95.5-101.9	86.7-100
Ca/P	1.22-1.60	1.25-2.00	1.29-1.75

theory of nutrient balance at multiple levels for animals and defined as a theory on changes, integration and regulation of the balance of nutrients from dietary and endogenous origin at the dietary level and all levels in an animal body. The essentials of this new theory are summarized as follows. First, the theory mainly covers four levels, i.e. dietary, digestive tract, liver and product tissues levels. Among these multiple levels, nutrient balance at the dietary level is a starting point and has an overall influence on nutrients balance in an animal body. There is a complex situation for a nutrient balance at each level, and there are interactions between different levels of nutrients balances and also between the dietary level and the whole body level. Second, there are three kinds of nutrient balances, i.e., internal balances of a nutrient, as well as bilateral balances between different nutrients or between metabolite balances. Third, nutrient balances are a dynamic and self-regulating mechanism in animals involving nutrient metabolism. Fourth, animal's living and growth require nutrient balances at all levels from the diet to the whole body. Different physiological targets have different extent of nutrients balances. Fifth, any value of nutrient balances is a range instead of a fixed one. Sixth, regulation of nutrient balances in an animal body plays an important role in nutrient partitioning or re-partitioning, enzyme synthesis, gene expression, protein synthesis, and endocrine balance.

2. A series of parameters for evaluating the nutrient balances at all levels has been developed. For example, the series of parameters for ruminants consist of three parts, i.e. the dietary, digestive tract, and metabolism levels. At the dietary level, the following parameters are selected: RDP/RUP, SP /RDP, lys/Met, ADF/NDF, NFC/NDF, Forage NDF/RDS, Starch/NDF, NFC/RDP, CP/NE<sub>L</sub> and Ca/P. A series of parameters for evaluating nutrient balances for lactating cows are given in Table 2. At the digestive tract level, metabolizable glucose (MG), metabolizable lipogenous substances (MLS), and metabolizable protein (MP) are suggested to evaluate nutrient balances. MG, MLS, and MP are generally called energy-yielding substances.

MG is defined as total amount of digestible glucose of feedstuff origin that can be provided for further use in metabolism, after digested and absorbed by animals. The formula for calculating MG is:  
 $MG = POEG + BSEG = 0.09K_1 \cdot Pr + 0.9K_2 \cdot BS$

Where POEG is the glucose amount provided by propionate from rumen fermentation (Pr, mmol/d) and transformed in the liver; BSEG is the glucose amount provided by bypass-starch (BS, g/d) and absorbed; K<sub>1</sub> and K<sub>2</sub> are absorption ratios for propionate and starch, respectively.

MLS is defined as total amount of utilizable fatty acids originated from acetate, butyrate and bypass-lipid of feedstuff origin, that can be provided for further use in metabolism, after digested and absorbed by animals. The formula for calculating MLS is:

$$MLS = 0.72 \cdot k_1 \cdot Ac + 1.8 \cdot k_2 \cdot Bu + 1.14 \cdot k_3 \cdot Fat$$

Where k<sub>1</sub>, k<sub>2</sub> and k<sub>3</sub> are absorption rates for acetate, butyrate and bypass-lipids, respectively; Ac, Bu are production rates of acetate and butyrate in the rumen (mmol/d); Fat is bypass-lipid amount (mmol/d, expressed as total fatty acids). Definition and calculation formula for MP were obtained from AFRC (1993) (6). An optimum ratio of MG, MLS and MCP in ruminant diets is an essential prerequisite for better utilization of dietary energy.

3. The metabolism level includes the use of substrates for synthesis of glycogen, lipids, and amino acids. The series of parameters for monogastric animals have been studied extensively (1). It should be emphasized that data on nutrient flux in the body, instead of concentration data, be considered a top priority, when each parameter is calculated. A new technique for evaluating dietary nutrient balances has been developed, which has two distinct features: parameter multiplicity and integrity. In order to reflect these two features, two kinds of equations were proposed:

$$DNBI = \{ \sum (1 - (N1 - X1)/N1) + \sum n2 + \sum (1 - (X3 - N3)/N3) \} / (n1 + n2 + n3) \text{ ---- (1)}$$

Where, DNBI----diet nutrient balance index

N1—the lower limit of a parameter

N3—the upper limit of a parameter

n1 —number of the lower limits of parameters

**Table 3.** Comparison of Nutricinomics with traditional single nutriline theory

Traditional single nutriline theory	Nutricinomics
Single nutriline	Components with multi- nutrines
Emphasizing the function of a nutriline	Emphasizing integrative functions and combination of multi- nutrines
Technology is focused on extraction and utilization of a nutriline	Technology is focused on studying and developing nutricinomics products

n3—number of the upper limits of parameters

n2—number of between the upper limit and the lower limit of a parameter

Equation (1) was successfully used for evaluating dietary nutrient balances of lactating cows.

$$AABI = \sqrt[n_2]{\prod_{i=n_2}^{n_3} \left[ 1 - \frac{AAAi - IAAi}{IAAi} \right]} \quad (2)$$

Where AABI -----amino acid balance index

AAAi----- i amino acid in an absorptive amino acid into the small intestine as a relative ratio to lysine

IAAi----- i amino acid in an ideal amino acid pattern as a relative ratio to lysine

Equation (2) can be used for evaluating internal balances of nutrients, such as dietary amino acids and fatty acids. In the future, there are three aspects for the study on the theory of nutrient balance: a) changes of nutrient balances in at diet-digestive tract-liver-product tissue levels and between the levels and their integrations; regulatory mechanisms responsible for nutrient balances at different levels in the animal body and developing a system of parameters for evaluating nutrient balances at all levels and manipulation technology.

## 7. NUTRICINOMICS PRODUCTS AND TECHNIQUES

During the past 20 years, due to the occurrence of antibiotic resistance and residue problem in animal products, scientists around the world have been struggling to find alternatives, preferably from natural resources. More and more studies on plant extracts for an antibiotic alternative have been conducted. However, the mode of thinking of the studies is still degenerated into analytics-reductionism. To counter this tendency, De-Xun Lu advanced the new concept “*nutricinomics*” in 2004 . By “*nutricinomics*”, we mean studies on interactions among a variety of nutrines in feedstuffs of natural origin and on optimum formulation and the integrative functions of the nutrines in man-made feed products. Comparison of nutricinomics with traditional single nutriline theory is given in Table 3.

Advancement of nutricinomics theory is a significant development in feed science studies, which especially carries the study and development of plant extract products to a new stage. The nutricinomics theory still has a long way to go. In the future, the following three important tasks should be addressed.

1. Study on functions, mechanisms, and applications of currently available and successful nutricinomics products (e.g., yeast culture). By means of NMR spectroscopy and chromatography linked to mass spectrometry, the entirety of multi-nutrines is studied and draws specific profiling of multi-nutrines in products and further studies on biological functions of interactions between the multi-nutrines and metabolites in animals.

2. Studies on applied techniques necessary to the nutricinomics products, such as developing integrated techniques system based on associated effects between multi-nutrines and other dietary nutrients. It is necessary to study on feeding values of nutricinomics products and to develop rapid and precise analytical technique for multi-nutrines.

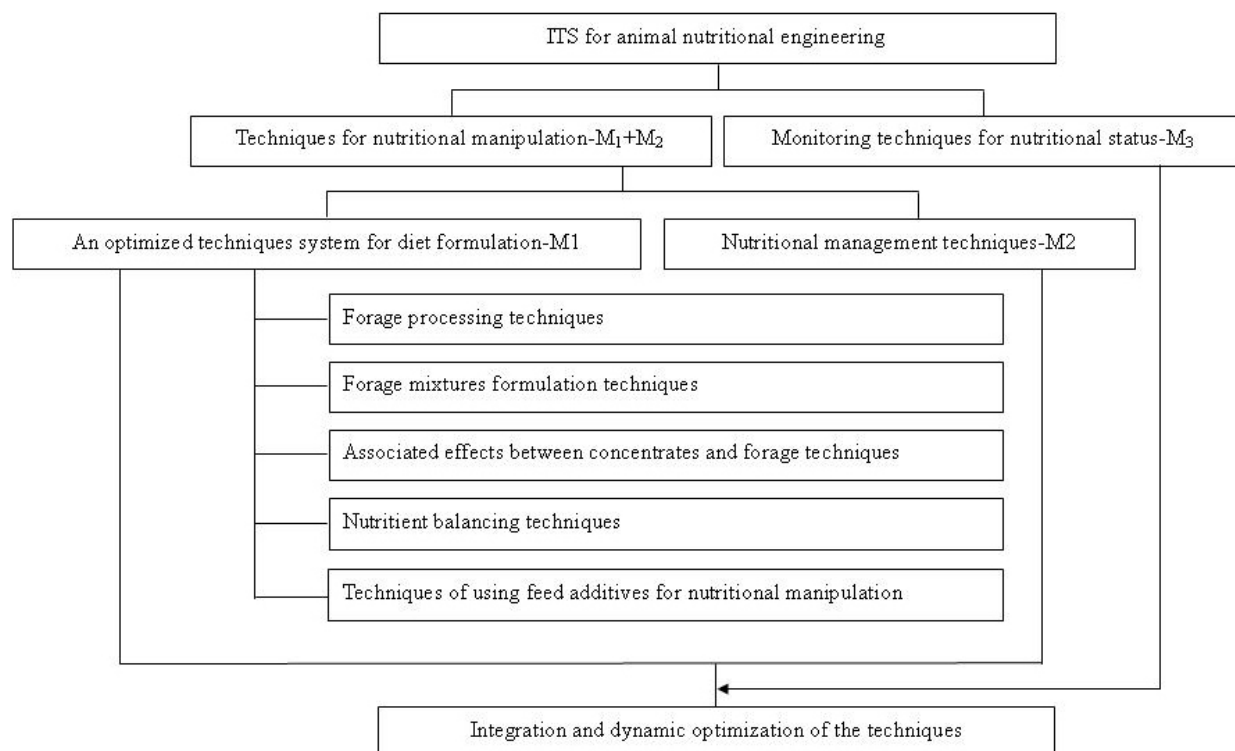
3. To enhance development of new nutricinomics products, including plant extracts, microbial fermentation products and other biological resources products.

Advancement of the nutricinomics theory has significance not only for studying and developing nutricinomics products, but also for the application of omics theories and technologies in animal nutrition, which should push forward studies on nutrines in feedstuffs and the animal nutrition field. At present, the nutricinomics theory is still at its infancy, and there is an urgent need for more researchers to enrich and improve the theory. However, we are confident that the nutricinomics theory has a wonderful freshness and vitality as well as excellent potential for application in the future.

## 8. ANIMAL NUTRITIONAL ENGINEERING

Due to historical reasons known to all, the traditional techniques in animal nutrition have not been formed from the perspective of an integrated system, and have some significant limitations. For example, the applied techniques are limited to dietary formulation and feed processing and pay more attention to nutrient deficiency. Meanwhile, these techniques are used in feeding practice in a single-handed way. Although more techniques are used together, the associated effects between the techniques are largely ignored. Aimed at those limitations, a new integrated technique system has been advanced in systems-nutrition, which is called the integrated technique system (ITS) for animal nutritional engineering. Definition of the new integrated technique system is that a series of applied techniques is integrated and used to develop and adopt the system engineering of nutritional manipulation, according to the theory for nutritional manipulation in systems-nutrition.

The main contents of the new integrated technique system are as follows: according to a certain target for nutritional decision, a series of applied nutritional



**Figure 1.** A schematic diagram of ITS for animal nutritional engineering.

techniques is designed in an integrative plan with the aim of organizing and carrying out the system engineering of nutritional manipulation to achieve an optimum nutritional status and optimum performance of animals. The principle of integration of the applied nutritional techniques is to fully utilize positive associated effects between the techniques and to control and minimize negative associated effects. A schematic diagram of integrated technique system for animal nutritional engineering is given in Figure 1.

The ITS for animal nutritional engineering consists two types of nutritional techniques, i.e. techniques for nutritional manipulation ( $M_1+M_2$  techniques) and monitoring techniques for the nutritional status ( $M_3$  techniques). The former ( $M_1+M_2$  techniques) also consists of two types of nutritional techniques, i.e., an optimized technique system for dietary formulation ( $M_1$  techniques) and nutritional management techniques ( $M_2$  techniques). In comparison with the traditional techniques, the ITS for animal nutritional engineering has several features:

1. Nutritional manipulation is given priority. This is a basic difference from the traditional techniques which pay more attention to nutrient deficiency.
2. Overall techniques and system-integration are an innate character of the ITS for animal nutritional engineering. This type of techniques puts more emphases on the associated effects between the techniques to seek the highest effect.

3. Use of monitoring techniques for the nutritional status as a tool to evaluate the integration extent.

4. Dynamic optimization must be adhered in design and carrying out this technique system.

The ITS for nutritional engineering of dairy cows has been used in dairy feeding practice successfully in China (7-12). This technique system has several innovations, such as putting forward a new target for decision of feeding dairy cows and three types of nutritional techniques ( $M_1$ ,  $M_2$  and  $M_3$ ) for integration; advancing a techniques integration and dynamic optimization modes for nutritional manipulation of dairy cows. It should be indicated that the optimized technique system for dairy diet formulation is noted for the most innovative characteristics. The more details can be found in a book entitled "Basis and Application of Nutritional Engineering of Dairy Cattle" published in 2012 (7).

## 9. CONCLUDING REMARKS

With the lapse of time, the limitations of the traditional scientific system in animal nutrition have been more and more evident, as recognized for the past classification of nutritionally essential and nonessential amino acids (13,14). The times are calling for innovation to revise the traditional scientific system. Much evidence shows that the key to innovation in the scientific system of animal nutrition is changing the mode of thinking. In recent years, we have proposed a new scientific system of systems-nutrition and our approach has yielded some

significant achievements, including a) theoretical research in the microcosmic nutrition field, b) research of the theory of nutrient balance at multiple levels, c) developments of nutraceuticals products and techniques, and d) developments of system-integrated techniques for animal nutrition engineering. Although systems-nutrition is still in its infancy, this concept has already opened up a new way to further develop the animal nutrition discipline. In fact, systems-nutrition will provide a state-of-the-art picture of where animal nutrition will stand in the future, and will also identify main areas of new research and applications of the new techniques.

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**Abbreviations:** ITS, integrated technique system; MG, metabolizable glucose; MLS, metabolizable lipogenous substances; MP, metabolizable protein.

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