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Perspective

Autocatalysis in Biological Systems

Chetan J. Gadgil and B. D. Kulkarni
Chemical Engineering and Process Development Division, National Chemical Laboratory, Pune, India

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Introduction

An autocatalytic process is one where the product enhances the process rate. Specific autocatalytic processes have been observed and investigated in the context of chemical reactions and reaction systems. Several reactions, for instance the iodate-arsenite reaction[1] have been thoroughly studied. Recently the phenomenon of chiral autocatalysis has been observed and analyzed.[2] At a "cell" scale, efforts toward the development of chemical self-replicating systems with autocatalytic reactions have been reported.[3]

An extended form of autocatalysis is a system of coupled reactions, such as the Belousov-Zhabotinsky reaction and the Oregonator, where the positive effect of the products of any one reaction on the rate of that reaction is indirect. For instance, the product of the first reaction may enhance the rate of another reaction whose product in turn enhances the rate of the first reaction. Such indirect autocatalytic effects will be referred to as positive feedback loops. The analysis of positive feedback loops is an integral part of the study of autocatalytic reactions.

The large body of quantitative data in biology has enabled the analysis of biological processes using chemical reaction engineering principles. In this Perspective, we discuss autocatalytic processes observed in the biological sciences from a mathematical modeling/chemical reaction engineering perspective. The review is organized on the basis of the scale of the process, from reactions involving a single chemical entity to processes at the ecology scale. Mathematical analyses of these processes are summarized and common themes such as multiple steady states and robust switching behavior emerging from the analysis at various scales are discussed. The review concludes with a discussion of current challenges and suggested directions for further study. As autocatalysis is extensively observed in every scale of biological processes, the overall approach is illustrative rather than comprehensive.

Autocatalytic processes in biology present certain features that chemical engineers are well-equipped to tackle. The first is the intricate control process coupled to biochemical transformations, with or without spatial variation, that have been studied in chemical engineering science in the context of chemical reaction engineering and process control. The other feature is interconnections between processes at different scales, which has been studied in the context of multiscale phenomena in chemical engineering. Through this perspective, we hope to draw attention to the challenges in these aspects of analysis of biological systems through examples of biological processes that exhibit such complex multiscale autocatalytic behavior.

Correspondence concerning this article should be addressed to C. J. Gadgil at cj.gadgil@ncl.res.in.

Autocatalytic Biological Processes

The study of autocatalytic biological processes can be organized in many ways: based on the system length scale, or time scale, or the taxonomic class of the organism. We have chosen to group autocatalytic processes based on the level of cellular complexity involved, which roughly correlates with the length scale of the process. An illustration of the various scales is shown in Figure 1. We start with single reaction processes and, following an increasing level of organization, discuss intracellular or reaction network level processes, processes which involve communication that crosses the outer boundary of the cell, tissue or organ level processes that involve transport of chemicals across multiple cell-lengths, organism-scale processes, where organ systems are involved, community level processes and finally ecology or biosphere-level processes. It should be noted that there are interactions across scales, as seen in the arrow going from the biosphere level process to the single molecule level process, which denotes changes in single molecules or DNA sequences occurring due to evolutionary pressure resulting from environmental conditions. Similarly, in the context of infectious diseases, cell-level processes affect and are affected by interactions between individuals and communities, as well as the environment. It is reasonable to assume that processes at each level of organization influence and are influenced to different extents by processes at every other level of organization shown in Figure 1.

Single-reaction scale autocatalysis

Autocatalytic single-reaction processes have been reported for folding and cleavage events, primarily for molecules whose active forms catalyze the same process. For example, the protein FKBP, a prolyl isomerase that catalyzes protein

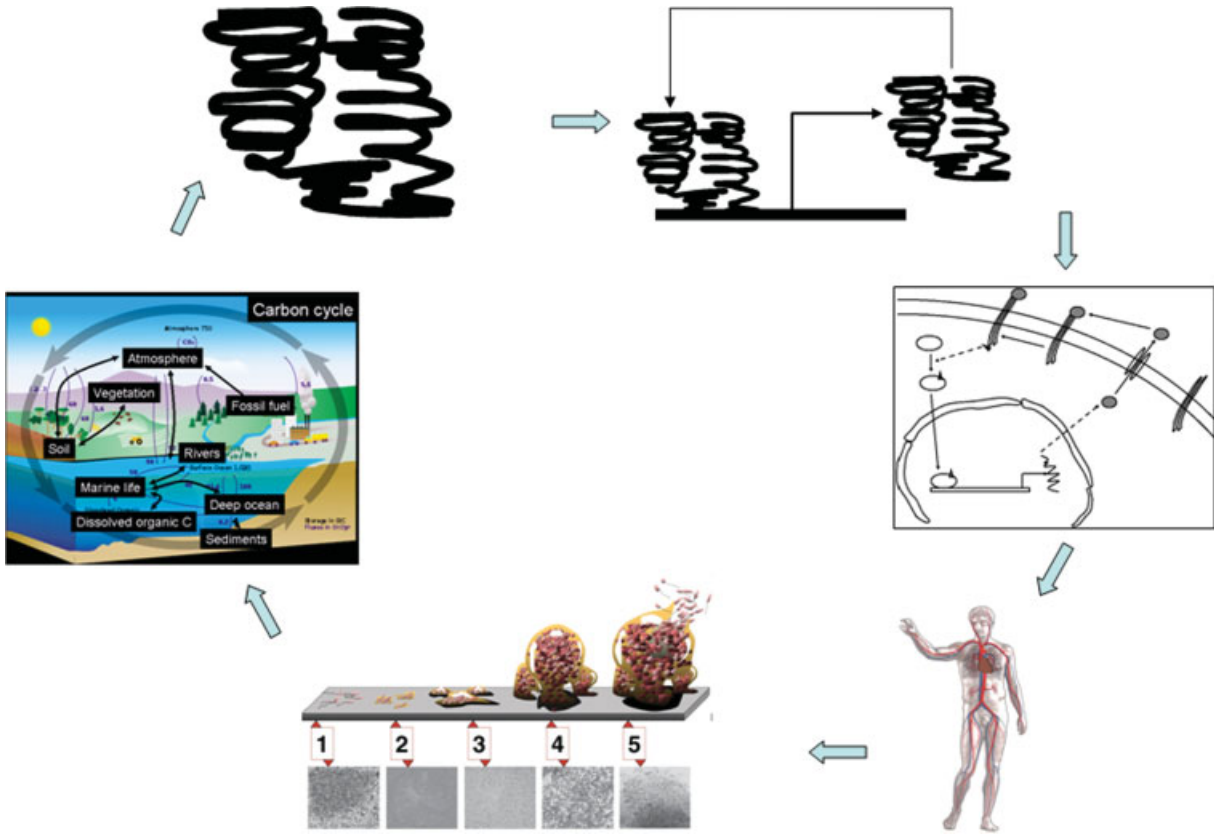

Figure 1. Autocatalysis at various scales: single molecule folding, autogeneous regulation, intracellular signaling pathways, organ systems, collective motion and ecological scales.

Evolution as a response to the environment results in changes in the structure and function of single molecules. Not shown are criss-crossing links that indicate the effect of intracellular signaling to community behavior, or single molecule folding to population dynamics for instance as seen in the effect of unfolded proteins in prion disease epidemiology. Figures except single molecule and autogeneous regulation are from wikipedia.com.

folding, catalyzes its own folding.[4] In prion disease, exponential growth is associated with autocatalytic fission of membrane-bound protein aggregates. This is a form of "conformational autocatalysis",[5] where a misfolded form of a protein induces a similar misfolding.

Another kind of proteins undergoing autocatalytic processing are the proteases, which are proteins that catalyze the cleavage of other proteins. Some proteases such as the metalloprotease Mpl of *Listeria monocytogenes*, and the apoptosis pathway enzyme Procaspase-3 are produced as a longer protein that exists in a proenzyme (inactive) form. The protease function is activated upon proteolytic cleavage by the active forms. Thus the product of the proenzyme cleavage reaction catalyzes the same reaction. An example of the extension of this process to multiunit complexes is seen in the process of mammalian 20S proteasome biogenesis through autocatalytic proteolysis of some of its subunits.[6]

Reaction scale/Intracellular scale autocatalysis

Reaction-network scale autocatalysis takes the form of positive feedback loops where the products of a reaction enhance its rate indirectly through their participation in other reactions. Such positive feedback loops occur at several scales. At an intracellular scale, the simplest forms of such feedback are reactions where the translation product (protein) enhances the transcription rate of its own gene, thus, forming more messenger RNA (mRNA), and, therefore, increasing the rate of the translation reaction. Examples of such autogenous activation reactions include the activation of the expression of the gene *deformed* by its protein product, and self-activation of expression by the transcription factor TBP through interaction with its own promoter region. The transcriptional activation effect may be indirect, such as the activation of expression of the protein Patched by its active form through multiple intermediates. Several other examples of transcriptional activation by the products of the reaction catalyzed by the gene product are seen in the carbohydrate uptake systems including the lactose, galactose[7] and maltose regulatory systems. In these systems, transcriptional activation results in the formation of proteins that increase intracellular levels of the carbohydrate (or a metabolite), which in turn enhances the transcriptional activation.

Individual pathways can be coupled through interpathway positive feedback loops. For instance, the positive coupling between the Wnt and Erk pathways enables the maintenance of an activated state without the requirement of a persistent

extracellular signal. Autocatalysis in the form of positive feedback loops is also an integral part of several other intracellular processes. Among the most important is the process of cell division. The mitosis reactions include a pathway that makes the mitosis promoting factor activation autocatalytic. Positive feedback sharpens the transition from the anaphase, the "anaphase switch". Other oscillatory processes including circadian oscillators also contain positive feedback loops.

Autocatalytic loops are frequently observed in circuits responsible for switching cellular states. Several positive feedback loops control stem cell stability and differentiation, resulting in bistability.[8] Stem cell fate decisions in response to leukemia inhibitory factor (LIF) involve positive feedback loops controlling expression of LIF signaling pathway constituents. Another cell fate decision, the myeloid progenitor differentiation into macrophages or neutrophils, is also controlled by a positive feedback loop. In plants, vein or inter-vein cell type specification is mediated by a positive feedback loop that is part of the bone morphogenetic protein signaling pathway. Positive feedback loops are also present in the regulatory pathways controlling lineage commitment of different types of blood cells during hematopoiesis,[9] white/opaque switching of cell types in the fungus *Candida*,[10] and the initiation of sporulation in *Bacillus subtilis*.[11]

This switching effect results from the ability of positive feedback loops to allow for the possibility of multiple stable steady states, and the cell switches from one state to another in response to a signal. If the switching is irreversible, this has the effect of converting a transient input signal into a permanent or long-lasting change in the cell state. This phenomenon is sometimes referred to as "cellular memory". The involvement of positive feedback loops in cellular memory circuits has been seen for instance in the galactose utilization system that tunes the response to galactose concentrations[7] and in the EGF mediated signaling system. A positive feedback loop extends the single-cell expression lifetime of the protein Tat, which is a modulator of HIV-1 infection. Conversely, it has also been shown that artificially weakening the positive feedback shortens the Tat expression transient and biases the probability in favor of latency. Several other examples of memory[12] and the role of positive feedback loops in the memory process have been reviewed.

In addition to positive feedback loops occurring naturally, scientists have introduced artificial constructs with components forming positive feedback loops. Synthetic circuits with autoregulatory elements have been used to engineer "cellular memory" in yeast, and to construct gene switches in yeast, *E coli*, mammalian cells, and plant cells.

Positive feedback loops operating at intercell scales

Signaling systems can occur at intercell scales through the formation of an extracellular entity that affects either the same cell (autocrine signaling), a cell in direct physical contact (juxtacrine), or a neighboring cell (paracrine). Autocatalytic loops are seen in all three forms of signaling. Autocrine feedback results in a sustained response to a transient signal, for instance, the MAPK pathway activation response to short pulses of ionizing radiation. Intercell signaling and positive feedback loops provide a robust spatial patterning mechanism.[13]

The same signal may elicit both autocrine and paracrine responses, sometimes through different pathways as are seen in the Wingless or Wnt positive feedback loops. The response to inflammation and pain involves the activation of the cyclooxygenase enzyme Cox-2, which acts on arachidonic acid and results in the formation of a number of prostaglandins (PGs). The Cox-2 enzyme is itself induced by the prostaglandins PGE_2 and PGJ_2. The hydrolysis of phosphatidylcholine to arachidonic acid and PGE_2/PGF2alpha formation are positively coupled processes. PGE_2 also induces the expression of the inflammatory factor IL-1alpha, which in turn induces Cox-2 and results in production of PGE_2. Thus, one component (Cox-2) can be involved in multiple positive feedback loops. T-cell receptor bistability involved in the adaptive immune response, and insulin-induced insulin receptor activation are other examples of positive feedback loops operating at an intercell scale.

Tissue/organ scale autocatalysis

Signaling at the tissue or organ scale occurs through a combination of autocrine and paracrine signaling loops and may involve active or facilitated transport of the signaling molecule. Positive feedback loops have been observed to be prevalent in patterning events occurring at this scale. In *Drosophila* wing dorsal-ventral boundary determination, a positive feedback loop *exists between boundary and nonboundary cells*.[14] In *Drosophila* imaginal disc patterning, the proteins Fused and Smoothened mutually enhance activities, and make the system resistant to fluctuations of the level of receptors for the morphogen Hedgehog.

In vertebrates, the Sonic hedgehog and Fibroblast growth factor (FGF) positive signaling loop determines distance between elements of the developing limb.[15] In plants, leaf vein patterning results from positive feedback between auxin and its transporter.[16] Such loops have also been implicated in *Arabidopsis* epidermis and distal root tip[17] patterning.

Positive feedback is important in defining cell identities and switching cell states that result in organ-scale changes. In neural integrators, the leading hypothesis for the mechanism leading to the processing of transient inputs to generate persistent firing rates is positive feedback between two populations of cells that constitute the integrator. The neuron-glia mutual activation positive feedback loop results in prolonging neuropathic pain. Branchless and Hedgehog positive feedback loops in the developing *Drosophila* brain regulates initiation of neuroblast division.

Organism level autocatalysis

Positive feedback at the organ system or organism level manifests itself in the form of collective decisions taken by a group of cells, or as systemic phenomena that affect multiple organs. In the *Dictyostelium* life cycle, the prestalk/prespore patterning in the slug stage is generated due to cell-restricted autocatalytic reaction coupled to inhibition by a substrate that gets depleted due to that autocatalytic reaction.[18] Prior to this stage, cell aggregation is influenced by the formation of cyclic AMP spiral wave, whose signaling mechanism includes positive feedback loops. Positive feedback in the circulatory sys-

tem affects multiple organs. Positive feedback loops contribute to the negative effects of angiotensin in increasing the blood pressure, and are involved in coagulation. In the clotting process, thrombin activation induces inflammatory factors that promote further thrombin activation.

Positive feedback can affect the behavior of individuals. A positive feedback loop between cognitions and emotions can lead to a breakdown when stress goes above a threshold.[19] Similarly, positive feedback loop between the adrenocortical stress response and aggressive behavior may contribute to the rapid escalation of violence in a stressful situation. A positive feedback loop has also been shown to influence the food intake process.

Community level autocatalysis

Positive feedback between individuals affects the behavior of communities. Autocatalytic models have been proposed for the growth of states and religion.[20] It has been shown to be a factor leading to a stable society. When an individual's altruism is used as a selection parameter, there is a competition to be more altruistic than others.[21] Positive feedback between predators and prey (through nutrient mineralization and prey transport) has a stabilizing effect on population dynamics, delaying or preventing the onset of oscillations.[22] Mutualism in communities is an example of positive feedback and may involve more than two entities, for instance in the ant-aphid-*Rabdophaga* loop, where ants protect aphids that feed on *Rabdophaga* induced rosette galls, and the abundance of all three species are shown to be positively correlated to each other. Ants protect the aphids from predators and in turn derive nourishment from the aphids. The exact mechanism of the positive effect of the ants and aphids on the *Rabdophaga* induced galls is unknown. Positive feedback between environmental fluctuations and group response has been proposed as a mechanism where the group enhances the fluctuation so that it is beyond the capacity of the response of individual "cheats", and, hence, limits the reproductive capability of such cheating individuals. Positive feedback loops have been shown to be important in quorum sensing pathways.[23] Positive feedback implemented in robots through a sensor that allows perception of average group motion results in emergent coordination, i.e., the collective succeeds in a task whereas individuals fail.

Ecosystem level autocatalysis

Examples of positive feedback and its importance at ecological and evolutionary scales have been reviewed.[24] Positive feedback between deglaciation and resultant warming may be the explanation for abruptness of deglaciation events.[25] A positive feedback loop exists between glacier melt rate and ice velocity,[26] and between seismic activity and seismic release.[27] Millennial scale warm and cold events occur because of a positive feedback loop between moisture transport across Central America, and salinity in the North Atlantic ocean.[28] A positive feedback between water and vegetation in semiarid lands results in the formation of spatial vegetative cover patterns.[29]

Mathematical analysis

Mathematical modeling and analysis of several autocatalytic systems has been carried out, and general themes underlying many autocatalytic systems have been identified. Mathematical models for several specific systems have been developed and simulated. For instance, the switching behavior of autocatalytic systems has been explored through mathematical models for a wide range of biological systems including the G-protein signaling pathway, oocyte maturation, budding yeast pheromone response, competence in *Bacillus subtilis*, Sonic hedgehog signaling in vertebrates, lac operon, MAP kinase cascade, fruit ripening, p53 activation, insulin signaling, persistence in bacterial populations, and long-term potentiation in neurons. Positive feedback loops involved in pattern formation have been explored through specific models of patterning during budding, regeneration and transplantation in *Hydra*, anterior-posterior axis patterning in *Drosophila*, models for interpretation of morphogenetic gradients based on autocatalysis and competition, and studies on the effect of autocatalysis on polarity and self-organization.

From the analysis of these specific systems and through the use of dynamical systems theory, certain properties of autocatalytic or positive feedback systems have been identified. It has been observed that a positive feedback loop is a necessary, but not sufficient condition for multistability for autonomous differential systems.[30] In particular, structural and parameter constraints for multistability in a model cell differentiation network have been identified. Criteria for instability of states in positive feedback systems have been identified.[31] Chaotic behavior has been observed in reactions with cubic and quadratic autocatalysis. Analysis of location and stability of monotone systems with single and multiple inputs and outputs has been carried out. It has been shown that monotone dynamical systems with or without time delays and only positive feedback loops have no stable oscillation, but do exhibit stable equilibria whose stability is independent of time delays.[32]

The presence of multiple steady states leads to switching behavior, and this phenomenon has also been explored in detail. A detailed analysis of switches including hysteresis, reversibility and role of stimulus in single-cells[7] and cell populations has been presented. It has been shown that memory that stores a transient input as the cell switches its state reversibly depends on the existence of a positive feedback loop, and abrogation of the loop makes the response transient as well.[33] However, it has also been shown that the hysteresis feature of the memory effect can be obtained without the presence of autocatalytic loops. In the context of patterning, mathematical analysis has been carried out identifying positive feedback loops as one of the required features of a reaction-diffusion network. However, alternate means of achieving reinforcement such as "mutual inhibition" without positive feedback or autocatalysis can generate intracellular polarity.

The presence of positive feedback loops have been shown to impart stability to a wide range of systems. Autocatalysis imparts robustness to the relative number of cell types produced in a differentiation process in a model where the cells produce trophic factors that act through a positive feedback-survival pathway. In a cell cycle control circuit, robustness of the negative feedback oscillator is due to the action of a positive feedback loop.[34] The presence of positive feedback loops

Table 1. Summary of Autocatalytic Processes

Starting Material	Product	Process	Phenomena	Reference
Single protein or protein aggregate	Active protein	Self-activation or deactivation	Autocatalysis at one timescale	4–6
Cell state 1	Cell state 2	Switching	Positive feedback at several timescales	8–11
Initial distribution	Spatiotemporal distribution	Pattern formation	Positive feedback and mass transport at several timescales	14–18
Individuals or groups	Coordinated or exaggerated reaction	Escalation of physiological and group behavior	Positive feedback at intra-organism and inter-organism scales	19–23
Ecological or geographical entity	Change in climate/ geographical feature	Abrupt ecological transition	Positive feedback, heat and mass transport at multiple length and time scales	25–29

allows buffering of propagated noise while maintaining sensitivity to long-term changes in input signals.[35] Interlinking of autocatalytic mutual inhibitory (double negative) loops leads to the system being more robust to parameter perturbations. In the context of patterning, presence of positive feedback loops results in robustness of the segment polarity network.

Discussion

The means through which a biological system acts in a coordinated manner to achieve a desired objective can be analyzed from the perspective of a component unit process such as autocatalysis or positive feedback. Other unit processes are negative feedbacks, feedforward signaling, transport/spatial sequestration, mechanotransduction, and electrochemical or charge regulation. In this review, we have shown through examples autocatalytic processes occurring at different scales. These examples can be analyzed in terms of the starting and final states of the system, and the nature of the process that causes this transition. Such a division of the examples used in this article to illustrate phenomena at different time and length scales is given in Table1. In these processes autocatalysis or positive feedback is thought to be the dominant principle used to bring about the desired biological outcome.

It is important to recognize that individual autocatalytic processes operate in the context of other bioreactions occurring at various scales from the intracellular to the ecosystem scale. This means that for a more complete understanding of the biological dynamics, the study of *coupled autocatalytic processes* is required. This may merely take the form of stiff systems with interlinked fast and slow autocatalytic loops. It has been shown that interlinked fast and slow loops result in rapidly inducible systems that are resistant to noise in the upstream signaling system.[36] From an evolutionary perspective, reflexive catalysts functioning in molecular aggregates may have been involved in the process of chemical evolution to the level of RNA or RNA analog self-replication.[37] This is an example of autocatalysis involving both the intramolecular kinetics required for folding to the functional 3-D (three-dimensional) structure, as well as autocatalysis at the longer time scale resulting in changes that optimize the function and allow for self-replication.

Autocatalytic processes are frequently part of complex signaling networks that also have negative feedback loops. In the microbe *Caulobacter*, the protein CtrA acts through two promoters active at different stages of the cell cycle to positively and negatively regulate its own expression. Limb outgrowth initiated by a positive feedback loop is then terminated by a negative feedback loop between the proteins Fibroblast growth factor and Gremlin. In the immune system, T-cell receptor ability to distinguish between closely related ligands and trigger effective signaling is based on a combination of positive and negative feedback loops. There are at least seven negative feedback and three positive feedback loops in p53 regulation. The meaning of this redundancy and implications of the relative degree of activation of each loop is yet to be understood, although it is thought to be important in understanding of cancer.[38] The analysis of autocatalytic processes that are components of *mixed systems*, such as the examples that contain both positive and negative feedback loops, is required for a more complete understanding of their role. It has been shown that autocatalysis in oscillatory systems with positive and negative feedback loops makes the system robust to parameter variations, and allows independent tuning of the frequency and amplitude. However, there is a lack of a general understanding of the contributions of positive feedback loops that are part of mixed systems. Mixed systems can be thought of as multidimensional extensions of Table 1, where the other dimensions allow for understanding of a particular biological process in terms of its component unit processes. For instance cell cycle reactions include negative feedback loops and multiple time scales in addition to positive feedback or autocatalysis. Circadian rhythms, in addition to all the aforementioned phenomena also include spatial transmission of signals on an organism-wide scale. For an understanding of a biological system at a level that enables predictions of the effect of changes in individual components on overall system dynamics, it is necessary to not only understand each individual unit process such as autocatalysis, but also its interactions with other unit processes as seen in mixed systems.

The presence of autocatalysis leads in many cases to multiple steady states. If more than one state is stable, the biological systems may switch from one stable state to another. This switching may be reversible or irreversible. The states may represent discrete (on-off) biological states. The stability of such steady states should be investigated from the discrete stochastic and the continuous deterministic perspectives to ensure that differing stability from the two perspectives does not lead to differences between the predictions of ordinary differential equation based continuous deterministic models and master equation based discrete stochastic models. Another property imparted because of the presence of positive feedback loops is the ability to transform transient stimuli into a long-lasting

response. The presence of autocatalytic loops has been shown to confer robustness to parameter and signal changes, and hence enables a reliable decision-making process. The stochastic simulation of a multispecies reaction model is computationally expensive, and a combination of model reduction and inexact stochastic simulations will have to be chosen such that the approximations involved in the model reduction and fast simulation processes do not fundamentally change the nature of the system. Several computational challenges arise due to the multiscale nature of biological processes, and due to the need for an ability to simulate complex dynamics, including those arising from the presence of positive feedback loops. There have been several recent attempts to address these issues, and a few of these include the application of "equation-free" approaches for biological problems,[39] or the development of hybrid schemes for "inexact", or exact but faster simulations of multiscale stochastic bioreaction networks.[40] Further discussion of the computational challenges and other methods being used or developed is beyond the scope of this review.

Conclusion

Autocatalytic and positive feedback loops are widely used by nature to impart properties such as robustness, multistability and controlled inducibility. Autocatalytic loops in biological systems operate in the context of coupled mixed processes occurring at several time and space-scales in the presence of intrinsic and extrinsic sources of noise. It is, therefore, important to dissect the role of autocatalysis in influencing the dynamics of biological processes. The future challenge will be to develop modeling and simulation methodologies to assess the impact of such interactions with the goal of a more complete understanding of the fascinating dynamics exhibited by biological systems.

Theory and methods developed in the study of chemical reaction engineering, heat and mass transport, and process control are well-suited for the study of complex and multiscale reaction systems, such as those seen in biological systems. Chemical engineers are trained to analyze complex reaction networks comprising of multiple reactions and multiple reactants such as those seen in traditional chemical processes such as combustion and oil refining. The same tools used in the development of model based predictive control strategies for chemical plants are needed for analysis of the control mechanisms used by biological systems. Theoretical developments such as model reduction and linear programming approaches are needed for the analysis of metabolic pathways. This training in the combination of chemical reaction kinetics, transport processes, control theory and optimization make chemical engineers uniquely positioned in the knowledge-space required for analyzing biological reaction networks such as the autocatalytic networks discussed in this Perspective.

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