A compositional account of motifs, mechanisms, and dynamics in biochemical regulatory networks *

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Introduction The genes, proteins, and RNA molecules that comprise living cells interact in complex, varied ways to sustain the cell throughout its lifecycle and respond to changes in its environment. Intensive experimental study of these interactions is distilled in an idealized form as *regulatory networks*, a kind of directed graph in which vertices represent molecules and edges represent interactions between molecules (Figure 0.1). The edges are labeled with a positive or negative sign according to whether the interaction is activating or inhibiting. Regulatory networks are the subject of a large body of experimental and theoretical work[Alo07; Alo19; TN10; TLK19]. Particular attention has been paid to *network motifs* [Alo07; TN10], the simple but functionally meaningful patterns that recur frequently in regulatory networks, and to quantitative *dynamics* [TLK19] that can be assigned to the networks.

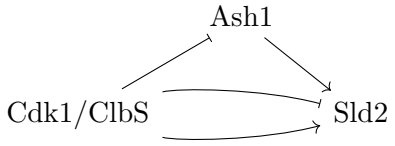

Figure 0.1: A small biochemical regulatory network: regulation of Sld2 by Cdk1 or ClbS with Ash1 as a predicted transcription factor. Adapted from Csikász-Nagy et al. [Csi+09, Figure 3C].

Although regulatory networks are simple enough to define mathematically—as directed graphs, possibly with multiple edges and loops, whose edges are assigned a positive or negative sign—important scientific concepts involving them, such as occurrences of motifs in networks and biochemical mechanisms generating networks, are often treated imprecisely. Likewise for relationships between regulatory networks and other mathematical models in biochemistry, particularly dynamical models based on ordinary or stochastic differential equations. Hence a first aim of this work is to put certain concepts and relations concerning regulatory networks on a firm mathematical footing.

Results We introduce a category-theoretic formalism for regulatory networks, using signed graphs to model the networks and signed functors to describe occurrences of one network in another, especially occurrences of network motifs. With this foundation, we establish functorial mappings between regulatory networks and other mathematical models in biochemistry. We construct a functor from reaction networks, modeled as Petri nets with signed links, to regulatory networks, enabling us to precisely define when a reaction network could be a physical mechanism implementing a regulatory network. Turning to quantitative models, we associate a regulatory network with a Lotka-Volterra system of differential equations, defining a functor from the category of signed graphs to a novel category of parameterized dynamical systems. This approach to quantitative parameters more closely follows the scientific and statistical traditions of viewing a mathematical model as requiring parameters that must be determined by experiment to uniquely identify a dynamical system. We extend this result from closed to open systems, demonstrating that Lotka-Volterra dynamics respects not only

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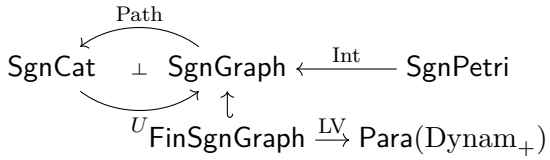
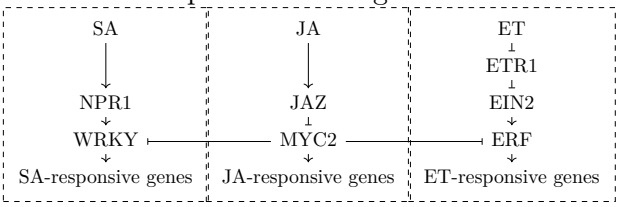
inclusions and collapsings of regulatory networks, but also the process of building up complex regulatory networks by gluing together simpler pieces. Formally, we use the theory of structured cospans to produce a lax double functor from the double category of open signed graphs to that of open parameterized dynamical systems. Throughout the paper, we ground the categorical formalism in examples inspired by systems biology. Key mathematical technologies of applied category theory include presheaves, slice categories, and structured cospans enable the development of this approach.

The major categories of this paper, and the functors between them, are summarized in the following diagram, where "LV" is the Lotka-Volterra dynamics functor. Most of the main results extend from closed systems to open systems, which compose by gluing along their boundaries.



When a plant perceives stress factors, it has three main biotic responses, called salicylic acid (SA) signaling, jasmonic acid (JA) signaling, and ethylene (ET) signaling. The stress response network can be computed as a composite of structured cospans describing the subnetworks.



The fact that behavior in a regulatory network can involve sequences of intermediaries, is captured by passing to signed functors, which allows us to capture many common biological motiffs as morphisms out of a representative object.

Given a signed graph A, regarded as a motif, an **instance** or **occurrence** of the motif A in a network X is a monic signed functor $A \rightarrowtail X$. The following tables summarizes common motifs.

Motif	Generic instance
Positive autoregulation	$L_+ \coloneqq \left\{ \bullet \circlearrowright \right\}$
Negative autoregulation	$L_- \coloneqq \left\{ \bullet \circlearrowright \right\}$
Coherent feedforward loop	$I_{++} \coloneqq \left\{ \bullet \rightrightarrows \bullet \right\}$
Incoherent feedforward loop	$I_{\pm} \coloneqq \left\{ \bullet \rightrightarrows \bullet \right\}$
Positive feedback loop	$L_{++} \coloneqq \left\{ \bullet \rightleftarrows \bullet \right\}$
Negative feedback loop	$L_{\pm} \coloneqq \left\{ \bullet \rightleftarrows \bullet \right\}$
Double-negative feedback loop	$L_{--} \coloneqq \{ \bullet \rightleftarrows \bullet \}$

Summary. Regulatory networks are a minimalistic but widely used tool to describe the interactions in biochemical systems. We have made the first functorial study of regulatory networks, formalized as signed graphs, and their connections with other mathematical models in biochemistry. Among such models, we have studied reaction networks, formalized as Petri nets with signed links, and parameterized dynamical systems, focusing on Lotka-Volterra dynamics.

Of many possible directions for future work, we mention a few. Lotka-Volterra dynamics are only one of numerous dynamics that could be considered as a canonical model for regulatory networks. Dynamics functors for regulatory networks could draw on other biologically plausible classes of dynamical systems. We also do not address how motifs in a regulatory network manifest in the continuous dynamics of that network.

This project fits into a broader program by applied category theorists and other scientists that aims to systematize, in a completely precise way, the language and methods of describing, comparing, and composing scientific models in different domains. Within biology, the field of systems biology has advocated for a holistic view of complex biological systems that emphasizes composition as much as reduction. We believe that category theory has a role to play in this endeavor by bringing mathematical precision to compositional and structural aspects of modeling that are traditionally thought to be outside the realm of mathematics.

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