Digital Logic and Signal Processing Computations with Molecular Reactions

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Dedication

To my wife, Yi-Hsuan, and my daughter, Madeline.

Abstract

Just as electronic systems implement computation in terms of voltage (*energy per unit charge*), molecular systems compute in terms of chemical concentrations (*molecules per unit volume*). Broadly, the field strives for molecular implementations of computational processes – that is to say processes that transform input concentrations of chemical types into output concentrations of chemical types.

In this dissertation, we present methodologies to implement digital signal processing (DSP) operations, such as filtering and signal transformation, and digital logic operations, such as latch and flip flop, with molecular reactions. Molecular reactions that produce time-varying output quantities of molecules as a function of time-varying input quantities are designed according to a DSP or logic specification. Unlike all previous schemes for molecular computation, the methodology produces designs that are dependent only on coarse rate categories for the reactions ("fast" and "slow"). Given such categories, the computation is exact and independent of the specific reaction rates. We first present a methodology for implementing DSP through a globally synchronous, locally asynchornous scheme we call the RGB scheme. We then present a general methodology for implementing synchronous sequential computation. We generate a four-phase clock signal through robust, sustained chemical oscillations. We implement memory el*ements* by transferring concentrations between molecular types in alternating phases of the clock. Thirdly, we propose a general methodology for implementing asynchronous sequential computation, including a method to schedule data flow for feed-forward systems and a method to implement systems with feedback loops. Finally, we present a methodology for systematic synthesis of various types of sequential digital logic. Given a system specification, a chemical reaction network is synthesized to perform the input/output logic functions.

Synthesized systems are concise and robust in that computation accuracy does not depend on specific values of rate constants. All designs are mapped into DNA strand displacement reactions and validated through transient simulations of the chemical kinetics at the DNA reactions level.

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Chapter 1

Introduction

In the nascent field of synthetic biology, researchers are striving to create biological systems with functionality not seen in nature. The field aims to apply engineering methods to biology in a deliberate way. Beyond engineering ends, such methods also provide a constructive means to validating new science. Understanding is achieved by constructing and testing simplified systems from the bottom up, teasing out and nailing down fundamental principles in the process. [1]

There has been a groundswell of interest in molecular computation in recent years [2, 3, 4, 5]. Just as electronic systems implement computation in terms of voltage (*energy per unit charge*), molecular systems can compute in terms of molecular concentrations (*molecules per unit volume*). Broadly, the field strives for molecular implementations of computational processes – that is to say processes that transform input concentrations of chemical types into output concentrations of chemical types. Some of the early work in the field discussed molecular solutions to challenging combinatorial problems such as the Hamiltonian Path Problem and Boolean Satisfiability [6]. In spite of the claims of "massive parallelism" – 100 Teraflop performance in a test tube! – such applications were never compelling. Chemical systems are inherently slow and messy, taking minutes or even hours to finish, and producing fragmented results.

The impetus is not to create computational systems per se. Molecular computation will never compete with conventional computers made of silicon integrated circuits for tasks such as number crunching. Rather, the ultimate goal is to create "embedded controllers" – cells and viruses that are engineered to perform useful molecular computation in situ where it is needed, for instance for drug delivery and biochemical sensing. For example, consider a system for chemotherapy drug delivery with engineered bacteria. The goal is to get bacteria to invade tumors and selectively produce a drug to kill the cancerous cells. Embedded control of the bacteria is needed to decide where and how much of the drug they should deliver. The design of effective embedded controllers will entail computational processing, performed in terms of molecular reactions. A variety of computational constructs have been proposed [7, 8, 9, 10]. Our prior work includes constructs for logical operations such as copying, counting, comparing and incrementing/decrementing [11, 12, 13]; programming constructs such as "for" and "while" loops [14]; arithmetic operations such as multiplication, exponentiation and logarithms [12, 14]; and signal processing operations such as filtering [15, 16, 17, 18, 19, 20]. Such computational processing could take the form: "If molecular type X is present, produce molecular type Y" where X is, say a protein marker of cancer and Y is a chemotherapy drug. Or it could be more complicated: "If X is present and Y is not present, or vice-versa, then produce Z" (i.e., an exclusive-or function). Or it could be time-varying computation: "Produce an output quantity Y that changes as X changes, but more smoothly" (i.e., low-pass filtering). Exciting work in this vein includes [21, 22, 23].

The past few decades have seen remarkable progress in the design of integrated circuits for digital signal processing (DSP) for applications such as audio and video processing [24]. A typical signal processing operation produces an output signal by filtering or transforming an input signal. Examples are smoothing a signal with a moving-average filter and performing a fast Fourier transform (FFT). We aim to apply and extend this expertise to the domain of molecular computation. DSP with molecular reactions will be discussed through Chapters 3 to 5.

There have been deliberate attempts to bring concepts from digital circuit design into the field [25, 7, 8, 26, 27, 28, 29]. Prior work has established mechanisms for implementing specific computational constructs. Building on this prior work, we present a general methodology for implementing *digital logic* computation. We first present a robust bistable system to represent binary bits. We then present D latch and D flip-flop based on the bit representation. Details will be discussed in Chapter 6.

We bring a particular mindset to tackle the problem of synthesizing new biological functions. We tackle synthesis at a *conceptual* level, working with abstract molecular types. Working at this level, we implement computational constructs. Then we map the conceptual designs onto a specific chemical substrate – DNA strand displacement [30]. We target DNA-based computation via strand displacement as our experimental chassis. Our contribution can be positioned as the *front-end* of a design flow. The output of our methodology is a set of abstract molecular reactions. Soloveichik *et al.* have developed a "DNA assembler" [4]; this constitutes the *back-end*. They have shown that the kinetics of molecular reactions can be *emulated* with DNA strand displacements. Reaction rates are controlled by designing sequences with different binding strengths. The binding strengths are controlled by the length and sequence composition of "toehold" sequences of DNA. Different reaction rates can be easily realized by designing DNA strands with different toehold lengths [31]. They have shown that that any system consisting of unimolecular reactions (i.e., those with a single reactant) and bimolecular reactions (i.e., those with two reactants) can be emulated by such DNA strand displacement reactions.

1.1 Organization

The rest of this dissertation is organized as follows: in Chapter 2, we provide computational model and biochemical background on molecular computation. In Chapter 3, we describe a globally synchronous, locally asynchronous method for implementing DSP with molecular reactions. In Chapter 4, we present a fully synchronous design for implementing DSP, with a molecular oscillator as the global clock. In Chapter 5, we present a fully asynchronous design in which signals are transferred based on a self-timed handshaking protocol. In Chapter 6, we extend our systems to the field of sequential digital logic. Functions such as latching and flip-flopping are implemented with molecular reactions. Finally, in Chapter 7, we provide concluding remarks and discuss future research directions.

Chapter 2

Computational Model and Biochemical Background

2.1 Technology-Independent Model

One of the great successes of integrated circuit design has been in abstracting and scaling the design problem. The physical behavior of transistors is understood in terms of differential equations – say, with models found in tools such as SPICE [32]. However, the design of circuits occurs at more abstract levels – in terms of switches, gates, and modules. Many analogous levels of abstraction exist for biological systems. These range from molecular dynamics, to protein networks, to genetic regulatory networks, to signaling pathways, to complete cellular systems, to multicellular organisms.

We will discuss a particular level of abstraction, analogous in some ways to transistor netlists: molecular reactions. We will examine the abstraction from a design perspective: how can we synthesize molecular reactions that produce specific output concentrations of molecules as *a function* of input concentrations? A molecular system consists of a set of chemical reactions, each specifying a rule for how types of molecules combine. For instance,

$$X_1 + X_2 \stackrel{k}{\longrightarrow} X_3, \tag{2.1}$$

specifies that one molecule of X_1 combines with one molecule of X_2 to produce one molecule of X_3 . The value k is called the *rate constant*. We model the molecular dynamics in terms of *mass-action kinetics* [33, 34]: reaction rates are proportional to (1) the concentrations of the participating molecular types; and (2) the rate constant. Accordingly, for the reaction above, the rate of change in the concentrations of X_1 , X_2 and X_3 is

$$-\frac{d[X_1]}{dt} = -\frac{d[X_2]}{dt} = \frac{d[X_3]}{dt} = k[X_1][X_2],$$
(2.2)

(here $[\cdot]$ denotes concentration). Most prior schemes for molecular computation depend on specific values of the rate constants, which limits the applicability since the rate constants are not constant at all; they depend on factors such as cell volume and temperature. The results of the computation are not robust.

We aim for robust constructs: in our methodology we require only coarse values (fast, slow, *etc.*) for the kinetic constants. Given the coarse values for these constants, the computation is exact. It does not matter how fast the reactions are – only that all fast reactions fire faster than slow reactions do.

2.2 Technology Mapping

Given a specification of an abstract molecular reaction network that implements the requisite computation, the next step is to map it to specific molecular reactions. We describe a mapping to DNA strand-displacement reactions. The reader is referred to [4] for a detailed discussion of this mechanism. Here we illustrate with an example.

Consider the DNA strand-displacement reaction shown in Figure 2.1. Here a single strand of DNA X_1 replaces the top strand of a double-strand DNA L_i ; this generates a

double-strand DNA H_j and a single-strand B_j . (This reaction is reversible.) The top strand of H_j can be replaced by single-strand X_2 , generating a single-strand O_j . Then O_i replaces two of the top strands of the double-strand T_i , releasing X_3 . (Note that the strands L_i , G_i and T_i are "fuel" sources. It is assumed that there is an abundant source of these; the concentrations do not matter.) The signals are the concentrations of X_1 , X_2 and X_3 . This sequence of strand displacements implements the abstract chemical reaction:

$$X_1 + X_2 \xrightarrow{k} X_3,$$

Figure 2.1: An example of DNA strand displacement.

In [4] it is demonstrated that *any* system consisting of bimolecular reactions i.e., reactions with two reactants each, can be mapped to such DNA strand-displacement reactions. All of our designs consist of bimolecular reactions.

2.3 Simulation & Validation

Given a set of reactions at abstract molecular level, we first map it to DNA stranddisplacement reactions of the form shown Figure ??. We then generate system kinetic equations of the mapped DNA system and obtain the transient solution. Such simulations of the chemical kinetics provide a reasonably accurate prediction of the actual *in vitro* behavior [5].

Chapter 3

The RGB Scheme

This chapter discusses techniques for implementing DSP operations such as filtering with molecular reactions. From a DSP specification, we demonstrate how to synthesize molecular reactions that produce time-varying output concentrations of molecules as a function of time-varying input concentrations. We implement the operations through a "self-timed" protocol that transfers concentrations between molecular types based on the absence of other types. We illustrate our methodology with the design of a simple moving average filter as well as a more complex biquad filter.

The chapter is organized as follows. First, in Section 3.1, we give a detailed example: we present a biomolecular implementation of a two-tap moving average filter. Then, in Section 3.2, we present the general methodology for synthesizing DSP systems. To illustrate the general method, we provide a second, detailed example: a biomolecular implementation of a biquad filter. In Section 3.3, we present a general system synthesis flow. In Section 3.4, we provide simulation results. Finally, in Section 3.5, we conclude with some remarks about potential applications for this work.

3.1 Example: A Moving-Average Filter

A sequential system computes output values that are a function of the current input values as well as prior input values. Here "current" and "previous" refer to successive signal values that are supplied by some external source. Our system consumes the input molecular types, and so resets the input signal to zero. Our system accepts new input values only after the current output value is cleared, i.e., after some external source consumes all of the output molecular type.



Figure 3.1: Schematic of a two-tap moving average filter. configuration



Figure 3.2: The two-tap moving average filter in a three-phase configuration

We illustrate our design methodology with a detailed example: a finite impulse response (FIR) filter. An FIR filter is shown in Figure 3.1. This system computes a *moving average*: given a time-varying input signal X, the output Y is a smoother version of it. More precisely, the output is one-half the current input value plus one-half the previous value.

Our implementation consists of the following set of reactions. We present the reactions in their entirety and then provide the rationale for the design. We validate the design after mapping it to DNA strand displacement reactions. We present the simulation results in Section 3.4.

$$\begin{array}{rcl} 2S_r & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & 2S_r + r \\ 2S_g & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & 2S_g + g \\ 2S_b & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & 2S_b + b \\ R' + r & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & R' \\ G' + g & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & G' \\ B' + b & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & B' \end{array}$$

$$(3.4)$$

The molecular types corresponding to *signals* are X, A, C, R, G, B and Y. These are labeled in Figure 3.2. To elucidate the design, we color-code some of these types into three categories: Y and R in red; G in green; and X and B in blue.

In the group of reactions 3.1, the concentration of X is transferred to A and to C, a fanout operation. The concentrations of A and C are both reduced to half – scalar multiplication operations. The concentration of A is transferred to the output Y and the concentration of C is transferred to R. (The transfer to R is the first phase of a delay operation. We discuss this operation below.) Once the signal has moved through the delay operation, the concentration of B is transferred to the output Y. Since this concentration is combined with the concentration of Y produced from A, this is an addition operation.

The group of reactions 3.2 implements the delay operation. The concentration of R is transferred to G and then to B. Transfers between two color categories are enabled by the absence of the third category: red goes to green in the absence of blue; green goes to blue in the absence of red; and blue goes to red in the absence of green. The reactions are enabled by molecular types r, g, and b that we call *absence indicators*.

(We discuss these types below.) The absence indicators ensure that the delay element takes a new value only when it has finished processing the previous value.

In the group of reactions 3.3, molecules of types R', G', and B' are generated from the signal types that we color-code red, green, and blue respectively. The concentrations of the signal types remain unchanged. (These reactions appear to violate conservation of mass. In fact, when mapped to DNA reactions, there are external "fuel" types.) Meanwhile, R', G', and B' are consumed by external sinks, denoted by \emptyset . (When mapped to DNA, these reactions include "waste" types.) Here, all reactions are expressly designed to have two reactants; as discussed in Section ??, this permits us to map the reactions to DNA strand displacement reactions effectively. This generation/consumption process ensures that equilibria of the concentrations of R', G', and B' reflect the total concentrations of red, green, and blue color-coded types, respectively. Accordingly, we call R', G', and B' color concentration indicators. They serve to speed up signal transfers between color categories.

In the group of reactions 3.4, molecules of the absence indicator types r, g, and b are generated from external sources S_r , S_g , and S_b . At the same time, they are consumed when R', G', and B' are present, respectively. Therefore, the absence indicators only persist in the absence of the corresponding signals: r in the absence of red types; g in the absence of green types; and b in the absence of blue types. They only persist in the absence of these types because otherwise "fast" reactions consume them quickly.

Finally, the group of reactions 3.5 provides positive feedback kinetics. These reactions effectively speed up transfers between color categories as molecules in one category are "pulled" to the next by color concentration indicators.

Note that the concentration of the input X is sampled in the green-to-blue phase. We assume that an external source supplies the input. The output Y is produced in the blue-to-red phase. We assume that an external sink consumes these molecules.

3.2 General DSP System Synthesis

Building on the example in the last section, we present a general methodology for performing DSP with molecular reactions. DSP operations are specified in terms of four basic modules: *fanout*, *scalar multiplication*, *addition*, and *delay elements*. We discuss constructs for each of these modules. We illustrate the general design method with a second detailed example, a biquad filter.

3.2.1 Scalar Multiplier

Scalar multiplication performs the operation

$$y = \frac{c_2}{c_1}x$$

where c_1 and c_2 are constants. This operation is implemented by choosing reactions with the appropriate coefficients:

$$c_1 X \longrightarrow c_2 Y.$$
 (3.6)

Every time this reaction fires, c_1 molecules of X get transferred to c_2 molecules of Y. Once the reaction has fired to completion, i.e., fully consumed all molecules of X, the requisite operation of scalar multiplication is complete.

As discussed in the introduction, a constraint on our designs is that all reactions should be bimolecular reactions. Accordingly, c_1 should be a power of 2. Suppose $c_1 = 2^n$. Then Reaction 3.6 can be replaced by the set of reactions

We use the notation

to denote the collection of Reactions 3.7, where $c_1 = 2^n$.

3.2.2 Adder

Addition performs the operation

$$y = x_1 + x_2.$$

This operation is implemented by choosing two or more reactions with the same product:

Again, we choose bimolecular reactions instead of unimolecular transfers, such as $X_1 \xrightarrow{k_{\text{fast}}} Y$. *Y*. Once both of these reactions have fired to completion, the concentration of *Y* will be the former concentration of X_1 plus the former concentration of X_2 .

3.2.3 Fanout

The fanout operation duplicates concentrations. It is implemented by choosing a reaction producing several different products from a single reactant:

1

$$2X \xrightarrow{\kappa_{\text{fast}}} 2Y_1 + 2Y_2. \tag{3.9}$$

Once this reaction has fired to completion, both the concentration of Y_1 and the concentration of Y_2 will be equal to the former concentration of X.

A *transfer module* is a special case of a fanout module. It simply transfers a molecular concentration from one type to another:

$$2X \xrightarrow{k_{\text{fast}}} 2Y.$$
 (3.10)

Transfer modules are used to resolve type assignment conflicts.

3.2.4 Delay Element

Delay elements are at the core of digital signal processing. They stores signals values temporarily, allowing for iterative processing. We implement delay elements by transferring concentrations between molecular types based on the absence of other types. Each delay element DE_i is assigned three molecular types $R(ed)_i$, $G(reen)_i$ and $B(lue)_i$. It is implemented by the following reactions.

Phase 1 reactions:

$$\begin{array}{cccc}
b + R_i & \stackrel{\mathbf{k}_{\text{slow}}}{\longrightarrow} & G_i \\
G' + R_i & \stackrel{\mathbf{k}_{\text{fast}}}{\longrightarrow} & G_i
\end{array}$$
(3.11)

Phase 2 reactions:

$$\begin{array}{cccc} r + G_i & \stackrel{\mathrm{k}_{\mathrm{slow}}}{\longrightarrow} & B_i \\ B' + G_i & \stackrel{\mathrm{k}_{\mathrm{fast}}}{\longrightarrow} & B_i \end{array}$$

$$(3.12)$$

Phase 3 reactions:

$$\begin{array}{ll} g + B_i & \stackrel{\mathbf{k}_{\mathrm{slow}}}{\longrightarrow} & Computations \\ R' + B_i & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & Computations \end{array}$$
(3.13)

We use the notation

$$Delay(R_i, G_i, B_i, \{output_list\})$$

to represent Reactions 3.11, 3.12, and 3.13. Here, $\{output_list\}$ is a list of molecular types that B_i should be transferred to during Phase 3. In addition, system input X is labeled blue, therefore, reactions

$$\begin{array}{ccc} g + X & \stackrel{\mathbf{k}_{\text{slow}}}{\longrightarrow} & Computations \\ R' + X & \stackrel{\mathbf{k}_{\text{fast}}}{\longrightarrow} & Computations \end{array}$$
(3.14)

also fire in Phase 3. We use

$$Input(X, \{output_list\})$$

to represent these reactions.

A computation cycle, in which an input value is accepted and an output value is computed, completes in three phases. The input X is injected in Phase 2 and the output Y is collect in Phase 1. In each phase the signals are transferred from molecular types in one color category to the next. Computations, including scalar multiplication, addition, and fanout, are carried out in Phase 3, during the transfer from blue to red:

Computations
$$\stackrel{k_{\text{fast}}}{\longrightarrow} R_j.$$
 (3.15)

This is illustrated in Figure 3.3. The computation reactions fire much faster than the transfer reactions, so molecules of R_j are immediately produced from molecules of B_i . Thus, reactions in Phase 3 effectively transfer blue signals to red signals.

Note that R_j produced in Phase 3 will be a red type of any succeeding delay element DE_j along the signal path from DE_i . In Figure 3.4, R_1 and R_2 are red; G_1 and G_2 are green; B_1 and B_2 are blue. The multiplier is the computation that occurs between the delay elements. DE_2 is a succeeding delay element of DE_1 , so molecules of B_1 are transferred to R_2 in Phase 3.



Figure 3.3: The three-phase transfer scheme.



Figure 3.4: Cascaded delay elements.

For each delay element, the color concentration types R', G', and B' are generated and consumed in the following reactions:

$$2R_{i} \xrightarrow{k_{\text{fast}}} 2R_{i} + R'$$

$$2Y \xrightarrow{k_{\text{fast}}} 2Y + R'$$

$$2G_{i} \xrightarrow{k_{\text{fast}}} 2G_{i} + G'$$

$$2B_{i} \xrightarrow{k_{\text{fast}}} 2B_{i} + B'$$

$$2X \xrightarrow{k_{\text{fast}}} 2X + B'$$

$$2R' \xrightarrow{k_{\text{fast}}} \emptyset$$

$$2G' \xrightarrow{k_{\text{fast}}} \emptyset$$

$$2B' \xrightarrow{k_{\text{fast}}} \emptyset$$
(3.16)

So molecules of R', G', and B' are generated by types of the corresponding color categories; they are consumed by external sinks. The equilibrium levels of these three types are determined by total concentrations of all the red types, blue types and green types, respectively. Note that these reactions are in the "fast" category, since the color concentration types cannot lag the signal types.

We use

$$Conc(R', \{red_type_list\})$$
$$Conc(G', \{green_type_list\})$$
$$Conc(B', \{blue_type_list\})$$

to represent Reactions 3.16. For example,

 $Conc(R', \{R_1, Y\})$

represents

$$2R_1 \xrightarrow{k_{\text{fast}}} 2R_1 + R'$$
$$2Y \xrightarrow{k_{\text{fast}}} 2Y + R'$$
$$2R' \xrightarrow{k_{\text{fast}}} \varnothing.$$

For delay elements, the following reactions generate the absence indicator types r, g, and b:

$$2S_{r} \xrightarrow{k_{\text{slow}}} 2S_{r} + r$$

$$R' + r \xrightarrow{k_{\text{fast}}} R'$$

$$2S_{g} \xrightarrow{k_{\text{slow}}} 2S_{g} + g$$

$$G' + g \xrightarrow{k_{\text{fast}}} G'$$

$$2S_{b} \xrightarrow{k_{\text{slow}}} 2S_{b} + b$$

$$B' + b \xrightarrow{k_{\text{fast}}} B'$$

$$(3.17)$$

We use

$$Abs(S_r, S_q, S_b, r, g, b, R', G', B')$$

to represent these reactions.

Here r, g and b are continually and slowly generated. However, they only persist in the absence of the corresponding color-coded types, since they are quickly consumed by R', G', and B', respectively, if these are present.

All transfers are initiated by absence indicators and then sped up by the color concentration indicators. The transfers initiated by the absence indicators are slow and those initiated by the color concentration indicators are fast. This mitigates against "leakage", e.g., some transferring from G_i to B_i before all of transferring from R_i to G_i is complete.

Note that, in any system, there are only three color concentration indicators (R', G' and B') and three absence indicators (r, g and b), regardless of the number of delay elements. These types help enable and speed up signal transfers for all reactions in the corresponding color categories. Through these common indicators, the corresponding phases of all delay elements are synchronized: all the delay elements must wait for each to complete its current phase before they can move to the next phase.

3.2.5 Example of a Biquad filter

We illustrate our synthesis method with a second example, an infinite impulse response (IIR) biquad filter. Biquad filters are basic building blocks of modern DSP systems. Highly stable, high-order filters can be implemented by cascaded biquad blocks [24]. A biquad filter is shown in Figure 3.5 and the corresponding molecular types are labeled in Figure 3.6. It is realized by the following reactions.

Delay elements:

$$Delay(R_1, G_1, B_1, \{R2, F, C\})$$

$$Delay(R_2, G_2, B_2, \{H, E\})$$
(3.18)

System input:

$$Input(X, \{R_1, A\})$$
 (3.19)

Scalar multiplications:

$$Mult(A, Y, 8, 1)$$

$$Mult(C, Y, 8, 1)$$

$$Mult(E, Y, 8, 1)$$

$$Mult(F, X, 8, 1)$$

$$Mult(H, X, 8, 1)$$
(3.20)

Concentration indicators:

$$Conc(R', \{R1, R2, Y\})$$

$$Conc(G', \{G1, G2\})$$

$$Conc(B', \{B1, B2, X\})$$
(3.21)

Absence indicators:

$$Abs(S_r, S_g, S_b, r, g, b, R', G', B')$$
(3.22)



Figure 3.5: Schematic of the biquad filter.



Figure 3.6: The filter in a three-phase configuration.

3.3 Synthesis Flow

We present guidelines for an automated synthesis flow. The DSP system is represented by a block diagram G(V, E), where the vertex set V represents basic modules – scalar multiplication, addition, fanout and delay element – and the edge set E represents connections. Each edge e_i is assigned a molecular type. The concentration of this type represents the signal flowing through e_i . The system is synthesized as follows:

- 1. Each delay element $DE_i \in V$ is assigned three color-coded molecular types R_i , G_i and B_i . Here R_i corresponds to the input edge, G_i is the internal storage molecule type, and B_i corresponds to the output edge.
- 2. The system input and output are assigned types X and Y, respectively. (For simplicity, we only consider systems with a single input and a single output. However, the method easily generalizes to systems with multiple inputs and outputs.)
- 3. The incoming edges of each adder are assigned the same molecular type as the outgoing edge. With all the inputs assigned the same type, the system implicitly performs an addition operation: each reaction produces a concentration that is added to the sum.
- 4. If there are assignment conflicts, transfer modules are included. For instance, if an adder has been assigned two conflicting types T_1 and T_2 , say because its inputs are from different delay operations, then a transfer reaction is included:

$$2T_1 \stackrel{\mathrm{k_{fast}}}{\longrightarrow} 2T_2.$$

This reaction transfers the concentration of T_1 to T_2 .

- 5. Next, if there are any unassigned edges, these are assigned arbitrary molecular types (without creating conflicts).
- 6. With all edges assigned non-conflicting molecular types, reactions are generated for each vertex according to the template of Reactions 3.6 to 3.14.

7. Finally, the common indicator Reactions 3.16 and 3.17 are included.



Figure 3.7: A filter with two delay elements directly connected.



Figure 3.8: Molecular type assignment.

Figure 3.7 gives an example of transfer modules. Figure 3.7 shows a simple filter for time-interleaved input data. It contains two delay elements. Since these two delay elements are directly connected, a transfer module is included for converting B_1 to R_2 . Similarly, a second transfer module is included for transferring B_2 to Y, the molecular type for the adder. These molecular type assignments are shown in Figure 3.8.

For a DSP system with n delay elements, there are 3n+2 molecular types to represent the n delay elements as well as the system input and output. Accounting for the absence and color concentration indicators, there are an additional 9 molecular types. The number of intermediate types will vary according to system architecture.

3.4 Simulations

To validate our designs for the moving-average and biquad filters, we map the reactions presented in Sections 3.1 and 3.2 to DNA strand displacement reactions, using
the method in [4]. We generate the corresponding system of kinetic differential equations and simulate these. We use similar parameters to [4]: The initial concentrations of auxiliary complexes is $C_{max} = 10^{-5}M$ and the maximum strand displacement rate constant is $q_{max} = 10^{6}M^{-1}s^{-1}$. The rate constant for the "slow" reactions is set to $k_{\rm slow} = 5.56 \times 10^{4}M^{-1}s^{-1}$. For "fast" reactions it is set to $k_{\rm fast} = 3 \times k_{\rm slow}$. The initial concentrations of S_r , S_g , and S_b are set to 1nM.



Figure 3.9: The moving-average filter.

The simulation results for the moving-average filter are shown in Figure 3.9. The input is a time-varying signal concentration X with both high-frequency and low-frequency components. The output is a time-varying signal concentration Y. Molecules of X are injected and molecules of Y are collected from the system every 20 hours. The figure shows the theoretical output, i.e., an exact calculation of filtering, as well as simulation results.



Figure 3.10: The biquad filter.

We see that our design performs very well, filtering out the high-frequency component as expected. The simulated output concentration does not quite track the theoretical output concentration; it is higher than it should be for high input concentrations. The explanation for this is that, for high input concentrations, the reactions fire quickly, so the computational cycle completes early. Before the next cycle begins, some "leakage" of the output concentration occurs.

The simulation results for the biquad filter are shown in Figure 3.10. Here molecules of X are injected and molecules of Y are collected from the system every 50 hours. We supply step-like and impulse-like changes in X. The figure shows the theoretical output, i.e., an exact calculation of filtering, as well as simulation results. As expected, the system performs notch filtering.

The simulation results show that even for a ratio $\lambda = k_{\text{fast}}/k_{\text{slow}}$ as low as 3, the systems perform well. In fact, in experimental implementations of DNA strand displacement systems, a ratio λ greater than 1000 is readily achievable. When λ is close to 1, i.e., fast reactions are not much faster than slow reactions, the concentrations of the absence indicators r, g, and b are high even when the concentrations of R', G', or B' are high. Also, the computational modules slow down. Accordingly, the accuracy of the computation degrades.

3.5 Remarks

Comparison of the RGB scheme and CMOS technology is listed in Table 3.1. In RGB scheme, global synchrony is reached by absence-indication-driven RGB cycle; there is no global clock. Fanout operation in the RGB scheme requires additional reactions. On the contrary, addition operation is free. Molecular transfers are slow reactions, in RGB scheme while computations are fast reactions, which makes clocking the bottleneck in RGB scheme, instead of computations, as in CMOS circuits.

	RGB	CMOS	
Synchronization	RGB cycle	Clock	
Fanout operation	Not free	Free	
Addition	Free	Not free	
Bottleneck	Molecular transfers	Computations	
Fast operations	Computations	Clock setup/hold/margin	

Table 3.1: Comparison of RGB Scheme and CMOS Technology

The methodology presented in this chapter is *self-timed* and *asynchronous* in the sense that computational cycles only begin when all molecules of the output type Y are consumed by an external sink. The computation itself is essentially *rate-independent*, meaning that within a broad range of values for the kinetic constants, the computation is exact and independent of the specific rates.

An alternative strategy would be to use *clocking* to implement *synchronous* computation. We have presented such a strategy in [17]. In that work, we describe a strategy for generating a *clock signal* through robust, sustained chemical oscillations. We implement *memory elements* by transferring concentrations between molecular types in alternating phases of the clock.

Although pertaining to biology, the contributions are not experimental nor empirical; rather they are constructive and conceptual. Certainly, engineering complex new reaction mechanisms in any experimental domain is a formidable task; for *in vivo* systems, there are likely to be many experimental constraints on the choice of reactions. However, the techniques that we have presented here are robust and scalable. Such features could be transformative for applications such as drug delivery and metabolic engineering.

Chapter 4

The Synchronous Scheme

In Chapter 3, we implement the operations through a "self-timed" protocol that transfers concentrations between molecular types based on the absence of other types. Global synchrony is achieved by locally asynchronous reactions. In this chapter, we present a fully synchronous design for implementing DSP, with a molecular oscillator as the global clock.

The rest of this chapter is organized as follows. In Section 4.1, we present a design methodology for synchronous sequential computation, based on clocking with chemical oscillations. We implement memory elements – flip-flops – by transferring concentrations between molecular types in alternating phases of the clock. In Sections 4.2 through 4.4, we present three detailed design examples: an FIR filter, an IIR filter, and a four-point, two-parallel FFT. In Section 4.5, we present simulations. Finally, in Section 4.6, we conclude the chapter with a discussion of possible experimental applications and future directions.

4.1 Synchronous Sequential Computation

The general structure of our design is illustrated in Figure 4.1. As in an electronic system, our molecular system has separate constructs to implement *computation* and

memory. A clock signal synchronizes transfers between computation and memory. For the computational reactions, we refer the reader to prior work [16, 19, 12, 14]. Operations such as addition and scalar multiplication are straightforward. Operations such as multiplication, exponentiation, and logarithms are trickier. These can be implemented with reactions that implement iterative constructs analogous to "for" and "while" loops. (They do so robustly and exactly, without any specific dependence on the rates.) The main contribution of this chapter is a new method for clock signal generation and for implementing memory.



Figure 4.1: Block diagram of a synchronous sequential system.

4.1.1 Clock Generation

In electronic circuits, a clock signal is generated by an oscillatory circuit that produces periodic voltage pulses. For a molecular clock, we choose reactions that produce sustained oscillations in the chemical concentrations. With such oscillations, a low concentration corresponds to logical value of zero; a high concentration corresponds to a logical value of one. Techniques for generating chemical oscillations are well established in the literature. Classic examples include the Lotka-Volterra, the "Brusselator" and the Arsenite-Iodate-Chlorite systems [35, 36]. Unfortunately, none of these schemes are quite suitable for synchronous sequential computation: we require that the clock signal be symmetrical, with abrupt transitions between the phases.

Here we present a new design for an *n*-phase chemical oscillator $(n \ge 3)$. The clock phases are represented by molecular types P_1, P_2, \dots, P_n . First consider the reactions:

$$2S_1 \xrightarrow{k_{\text{slow}}} a_1 + 2S_1$$

$$2S_2 \xrightarrow{k_{\text{slow}}} a_2 + 2S_2$$

$$\vdots \qquad (4.1)$$

$$2S_n \xrightarrow{k_{\text{slow}}} a_n + 2S_n$$

and

$$P_{1} + a_{1} \xrightarrow{k_{\text{fast}}} P_{1}$$

$$P_{2} + a_{2} \xrightarrow{k_{\text{fast}}} P_{2}$$

$$\vdots$$

$$P_{n} + a_{n} \xrightarrow{k_{\text{fast}}} P_{n}.$$

$$(4.2)$$

In Reactions 4.1, the molecular types a_1, a_2, \dots, a_n are generated slowly and constantly, from source types S_1, S_2, \dots, S_n , whose concentrations do not change with the reactions. Here, all reactions are expressly designed to have two reactants; as discussed before this permits us to map the reaction to DNA strand displacement reactions effectively. In Reactions 4.2, the types P_1, P_2, \dots, P_n quickly consume the types a_1, a_2, \dots, a_n , respectively. Call P_1, P_2, \dots, P_n the phase signals and a_1, a_2, \dots, a_n the absence indicators. The latter are only present in the absence of the former. The reactions

$$P_{1} + a_{n} \xrightarrow{k_{\text{slow}}} P_{2}$$

$$P_{2} + a_{1} \xrightarrow{k_{\text{slow}}} P_{3}$$

$$\vdots$$

$$P_{n} + a_{n-1} \xrightarrow{k_{\text{slow}}} P_{1}$$

$$(4.3)$$

transfer one phase signal to another, in the absence of the previous one. The essential aspect is that, within the $P_1P_2 \cdots P_n$ sequence, the full quantity of the preceding type is transfered to the current type before the transfer to the succeeding type begins.

To achieve sustained oscillation, we introduce positive feedback. This is provided by the reactions

Consider the first three reactions. Two molecules of P_1 combine with one molecule of P_n to produce three molecules of P_1 . The first step in this process is reversible: two molecules of P_1 can combine, but in the absence of any molecules of P_n , the combined form will dissociate back into P_1 . So, in the absence of P_n , the quantity of P_1 will not change much. In the presence of P_n , the sequence of reactions will proceed, producing one molecule of P_1 for each molecule of P_n that is consumed. Due to the first reaction,

the transfer will occur at a rate that is super-linear in the quantity of P_1 ; this speeds up the transfer and so provides positive feedback.

Suppose that the initial quantity of P_1 is set to some non-zero amount, and the initial quantity of the other types is set to zero. We will get an oscillation among the quantities of P_1, P_2, \dots, P_n .

One requirement for clock in synchronous computation is that different clock phases should not overlap. More specifically, concentrations of molecular types representing clock phase "0" and clock phase "1" should not be present at the same time. To this end, we choose two nonadjacent phases, P_1 and P_3 in a four-phase oscillator, as the clock phases. For a clearer illustration, we use R(ed) to denote P_1 and B(lue) to denote P_3 .

Our scheme for chemical oscillation works well. Figure 4.2 shows the concentrations of R and B as a function of time, obtained through ordinary differential equation (ODE) simulations of the reactions 4.1, 4.2, 4.3 and 4.4. We note that the R and B phases are non-overlapping.



Figure 4.2: ODE simulation of the chemical kinetics of the proposed clock.

4.1.2 Memory

To implement sequential computation, we must store and transfer signals across clock cycles. In electronic systems, storage is typically implemented with flip-flips. In our molecular system, we implement storage and transfer using a two-phase protocol, synchronized on phases of our clock. Every memory unit S_i is assigned two molecular types D'_i and D_i . Here D'_i is the first stage and D_i the second.

The blue phase reactions are:

$$\begin{array}{ccc} B + D_i & \stackrel{\mathrm{k}_{\mathrm{slow}}}{\longrightarrow} & Computations + B \\ Computations & \stackrel{\mathrm{k}_{\mathrm{fast}}}{\longrightarrow} & D'_i. \end{array}$$

$$(4.5)$$

Every unit S_i releases the signal it stores in its second stage D_i . The released signal is operated on by reactions in *computational modules*. These generate results and push them into the first stages of succeeding memory units. Note that D'_j molecules will be the first stage of any succeeding memory unit S_j along the signal path from S_i .

The red phase reactions are

$$R + D'_j \stackrel{k_{\text{slow}}}{\longrightarrow} D_j + R. \tag{4.6}$$

Every unit S_j transfers the signal it stores in D'_j to D_k , preparing for the next cycle. For the equivalent of delay (D) flip-flops in digital logic, j = k. For other types of memory units, j and k can be different. For example, for a toggle (T) flip-flop, S_k is the complementary bit of $S_j: D'_j \longrightarrow D_k$ and $D'_k \longrightarrow D_j$ toggle the pair of bits in each clock cycle. The transfer diagram for our memory design is shown in Figure 4.3.

4.1.3 Computation

Scalar multiplication, addition and fanout operations are discussed in Section 3.2. In this section, we discuss how switches are implemented with molecular reactions.



Figure 4.3: The two-phase memory transfer scheme.

Switches

To implement switching functionality in our molecular design, we use two alternating selection signals. We generate these with a pair of D-flip-flops, as shown in Figure 4.4. If there is a non-zero initial concentration of S'_1 , then S'_0 and S'_1 will be "turned on" once every two cycles, in alternating fashion, starting with S'_1 . Note that it is S'_1 and S'_0 , not S_1 and S_0 , that enable the switches, because they are generated in the blue phase.

We could implement this computation with the following reactions, based on the signal transfer principles discussed above:

$$R + S'_{0} \xrightarrow{k_{\text{slow}}} S_{0} + R$$

$$R + S'_{1} \xrightarrow{k_{\text{slow}}} S_{1} + R$$

$$B + S_{1} \xrightarrow{k_{\text{slow}}} S'_{0} + B$$

$$B + S_{0} \xrightarrow{k_{\text{slow}}} S'_{1} + B$$

$$(4.7)$$

However, there is a problem with this implementation. Enabling signals S'_0 and S'_1 are transferred to S_0 and S_1 by R. It takes time to finish these transfers. Therefore, there

will always be overlapped R and S'_0/S'_1 . Since S'_0 and S'_1 should only be present during B phase, this overlapping causes computation errors.

To cope with this problem, we change Reactions 4.7 to

$$V + S'_{0} \stackrel{k_{\text{fast}}}{\longrightarrow} S_{0} + V$$

$$V + S'_{1} \stackrel{k_{\text{fast}}}{\longrightarrow} S_{1} + V$$

$$B + S_{1} \stackrel{k_{\text{slow}}}{\longrightarrow} S'_{0} + B$$

$$B + S_{0} \stackrel{k_{\text{slow}}}{\longrightarrow} S'_{1} + B$$

$$(4.8)$$

Here, V is the clock phase signal following B. S'_0 and S'_1 are quickly transferred to S_0 and S_1 right after B phase ends. With this modification, overlapping between S'_0/S'_1 and R is minimized. Clock phases and enabling switch signals are illustrated in Figure ??.



Figure 4.4: Generating the selection signals.

The transfer reactions enabled by S_1' or S_0' implement the switches.

4.2 A Finite-Impulse Response Filter

We first illustrate our design methodology with a detailed example: a finite impulse response (FIR) filter. An FIR filter is shown in Figure 4.6. This system computes a *moving average*: given a time-varying input signal X, the output Y is a smoother



Figure 4.5: Clock phases and selection signals.



Figure 4.6: A two-tap moving average filter.

version of it. More precisely, the output is one-half the current input value plus one-half the previous value.

To implement this FIR filter, Reactions 4.1 to 4.4 should be included to provide clock phase types. Again, we use P_1 and P_3 of a 4-phase clock as R and G.

Memory and computation are implemented by following reactions:

$$B + X \xrightarrow{k_{\text{slow}}} A + C + B$$

$$2A \xrightarrow{k_{\text{fast}}} D'_{1}$$

$$2C \xrightarrow{k_{\text{fast}}} Y$$

$$B + D_{1} \xrightarrow{k_{\text{slow}}} Y + B$$

$$R + D'_{1} \xrightarrow{k_{\text{slow}}} D_{1} + R.$$

$$(4.9)$$

In the set of Reactions 4.9, with clock phase B, input signal X is transferred to A and C, which are both reduced to half and transferred to D'_1 and Y, respectively. With clock phase R, D'_1 is transferred to D_1 . These reactions complete the memory and computation operations of the moving-average filter. Full list of reactions implementing the FIR filter is provided in Section A.1.

4.3 An Infinite-Impulse Response Filter

We illustrate our method with a second example, an infinite impulse response (IIR) biquad filter. Biquad filters are basic building blocks of modern DSP systems. Highly stable, high-order filters can be implemented by cascaded biquad blocks [24]. A biquad filter is shown in Figure 4.7. It is implemented by the following reactions.

$$B + X \xrightarrow{k_{\text{slow}}} A + D'_1 + B$$

$$B + D_1 \xrightarrow{k_{\text{slow}}} F + C + D'_2 + B$$

$$B + D_2 \xrightarrow{k_{\text{slow}}} H + E + B$$

$$(4.10)$$



Figure 4.7: A two-tap moving average filter.

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(4.11)

$$\begin{array}{cccc}
R + D_1' & \stackrel{\mathbf{k}_{\text{slow}}}{\longrightarrow} & D_1 + R \\
R + D_2' & \stackrel{\mathbf{k}_{\text{slow}}}{\longrightarrow} & D_2 + R.
\end{array}$$
(4.12)

In the set of Reactions 4.10, with clock phase B, signal X is transferred to A and D'_1 ; D_1 is transferred to C, F and D'_2 ; D_2 is transferred to H and E. In the set of Reactions 4.11, temporary signals A, C, E, F and H are multiplied by $\frac{1}{8}$ and transferred to either X or Y. In the set of Reactions 4.12, with clock phase R, signal transfers inside memory units take place. Full list of reactions implementing the IIR filter is provided in Section A.2.

4.4 A Four-Point FFT Design

We present a third design example, a four-point fast Fourier transform (FFT). The FFT operation is canonical in signal processing. It can have a parallel pipelined architectures for high throughput [24]. A block diagram is shown in Figure 4.8. The input signals are I_1 , I_2 , I_3 , and I_4 , respectively. The outputs are O_1 , O_2 , O_3 , and O_4 . There are two stages in this system, each containing two butterflies. There is a -jmultiplication between the two stages.



Figure 4.8: Block diagram of a 4-point FFT design.

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4.4.1 Direct Implementation



Figure 4.9: Block diagram of a 4-point FFT design, direct implementation.

A straight-forward implementation method is illustrated in Figure 4.9. Here, input signals are injected into the system as I. Inputs are then buffered by three delay elements, as the serial-to-parallel conversion. Outputs are available every four cycles.

In this system, signals are complex numbers. Both the real and the imaginary parts can be negative numbers. To represent the signals, each number X is assigned four molecular types X_p , X_n , X_p^* , and X_n^* . The first two are assigned to the real parts: X_p represents the positive component and X_n the negative component. The last two are assigned to the imaginary parts: X_p^* represents the positive component and X_n^* the negative component. Therefore, $X = [X_p] - [X_n] + j([X_p^*] - [X_n^*])$.

Adders are implemented by assigning input edges and output edges to the same molecular type [16]. Note that there are two negative input edges in the lower two adders. Signals from the negative input edge will be transferred to the opposite component. For example, M_1 is transferred to O_1 and O_3 as

$$2M_{1,p} \xrightarrow{\mathbf{k}_{\text{slow}}} 2O_{1,p} + 2O_{3,n}$$

$$2M_{1,n} \xrightarrow{\mathbf{k}_{\text{slow}}} 2O_{1,n} + 2O_{3,p}$$

$$2M_{1,p}^{*} \xrightarrow{\mathbf{k}_{\text{slow}}} 2O_{1,p} + 2O_{3,n}^{*}$$

$$2M_{1,n}^{*} \xrightarrow{\mathbf{k}_{\text{slow}}} 2O_{1,n} + 2O_{3,p}^{*}$$

$$(4.13)$$

or simply

$$2M_1 \stackrel{k_{\text{slow}}}{\longrightarrow} 2O_1 + 2O_3^-. \tag{4.14}$$

Also, for each number X, the reactions

$$\begin{array}{cccc} X_p + X_n & \stackrel{\mathbf{k}_{\text{fast}}}{\longrightarrow} & \varnothing \\ X_p^* + X_n^* & \stackrel{\mathbf{k}_{\text{fast}}}{\longrightarrow} & \varnothing \end{array} \tag{4.15}$$

are required. They cancel out equal concentrations of positive and negative components by transferring them to an external sink.

There is a -j multiplication in the system. It is implemented by

$$2M_{4,p} \xrightarrow{\mathbf{k}_{\text{fast}}} 2M_{4,n}'^{*}$$

$$2M_{4,n} \xrightarrow{\mathbf{k}_{\text{fast}}} 2M_{4,p}'^{*}$$

$$2M_{4,p}^{*} \xrightarrow{\mathbf{k}_{\text{fast}}} 2M_{4,n}'$$

$$2M_{4,n}^{*} \xrightarrow{\mathbf{k}_{\text{fast}}} 2M_{4,p}'$$

$$(4.16)$$

or simply

$$2M_4 \stackrel{k_{\text{fast}}}{\longrightarrow} 2M_4^{\prime-*} \tag{4.17}$$

which transfers real/imaginary parts to imaginary/real parts with opposite polarity.

Full list of reactions implementing the FFT unit is provided in Section A.3.1.

4.4.2 Two-Parallel Implementation

Another implementation method, the two-parallel implementation [37], is illustrated in Figure 4.10.

Assume that the system starts at clock cycle 1. The first two inputs are sampled in cycle 1; the last two inputs are sampled in cycle 2. The system generates the first and third outputs in cycle 3; it generates the other two outputs in cycle 4.



Figure 4.10: Block diagram of a 4-point FFT design, two-parallel.

There are four switches in this design. Each selects one of the two incoming signals alternatively in different cycles. We use Reactions 4.8 to implement them.

For example, at the n + 1st clock cycle, M_1 is transferred to O_1 and O_2 as

or simply

$$S_1' + M_1 \stackrel{k_{\text{slow}}}{\longrightarrow} O_1 + O_2^- + S_1'. \tag{4.19}$$

Based on the computational operations discussed above, we have the blue phase reactions

$$I_{1} + S'_{1} \xrightarrow{k_{\text{fast}}} D'_{1} + S'_{1}$$

$$I_{1} + S'_{0} \xrightarrow{k_{\text{fast}}} M_{1} + M_{2}^{-} + S'_{0}$$

$$I_{2} + B \xrightarrow{k_{\text{fast}}} D'_{2} + B$$

$$D_{2} + S'_{0} \xrightarrow{k_{\text{fast}}} D'_{1} + S'_{0}$$

$$D_{2} + S'_{1} \xrightarrow{k_{\text{fast}}} M_{1} + M_{2}^{-} + S'_{1}$$

$$D_{1} + B \xrightarrow{k_{\text{fast}}} M_{1} + M_{2} + B$$

$$M_{2} + S'_{1} \xrightarrow{k_{\text{fast}}} D'_{4}^{-*} + S'_{1}$$

$$M_{2} + S'_{0} \xrightarrow{k_{\text{fast}}} D'_{4} + S'_{0}$$

$$M_{1} + S'_{0} \xrightarrow{k_{\text{fast}}} D'_{3} + S'_{0}$$

$$M_{1} + S'_{1} \xrightarrow{k_{\text{fast}}} O_{1} + O_{2}^{-} + S'_{1}$$

$$D_{3} + B \xrightarrow{k_{\text{fast}}} O_{1} + O_{2}^{-} + S'_{0}$$

$$D_{4} + S'_{1} \xrightarrow{k_{\text{fast}}} D'_{3} + S'_{1}.$$
(4.20)

Note that S'_0 and S'_1 are generated in the blue phase. It is not necessary to list B if a reaction is enabled by S'_0 or S'_1 .

The red phase reactions are

$$R + D'_{1} \xrightarrow{k_{\text{fast}}} D_{1} + R$$

$$R + D'_{2} \xrightarrow{k_{\text{fast}}} D_{2} + R$$

$$R + D'_{3} \xrightarrow{k_{\text{fast}}} D_{3} + R$$

$$R + D'_{4} \xrightarrow{k_{\text{fast}}} D_{4} + R.$$

$$(4.21)$$

So the full design of the four-point, two-parallel FFT consists of Reactions 4.7, 4.20 and 4.21, together with the positive/negative canceling reactions as well as the clock generation reactions.

Full list of reactions implementing the FFT unit is provided in Section A.3.2.

4.5 Simulations

To validate our designs for the filters and FFT, we map the reactions presented in previous sections to DNA strand displacement reactions, using the method in [4]. We generate the corresponding system of kinetic differential equations and simulate these. We use similar parameters to [4]: The initial concentrations of auxiliary complexes is $C_{max} = 10^{-5}M$ and the maximum strand displacement rate constant is $q_{max} = 10^{6}M^{-1}s^{-1}$. The rate constant for the "slow" reactions is set to $k_{\rm slow} =$ $5.56 \times 10^{4}M^{-1}s^{-1}$. For "fast" reactions it is set to $k_{\rm fast} = 10 \times k_{\rm slow}$. The initial concentrations of S_1, S_2, \dots, S_n are all set to 1nM.

4.5.1 FIR

The simulation results for the moving-average filter are shown in Figure 4.11. The input is a time-varying signal concentration X with both high-frequency and low-frequency components. The output is a time-varying signal concentration Y. Molecules of X are injected and molecules of Y are collected from the system every 43.2 hours. The figure shows the theoretical output, i.e., an exact calculation of filtering, as well as simulation results.

We see that our design performs very well, filtering out the high-frequency component as expected. For high input concentrations, the reactions fire quickly, so the computational cycle completes early. Before the next cycle begins, some "leakage" of the output concentration occurs.

4.5.2 IIR

The simulation results for the biquad filter are shown in Figure 4.12. Here molecules of X are injected and molecules of Y are collected from the system every 43.2 hours. We supply step-like and impulse-like changes in X. The figure shows the theoretical output, i.e., an exact calculation of filtering, as well as simulation results. As expected,



Figure 4.11: Transient simulation result of the moving-average filter.

the system performs notch filtering. The simulation results show that even for a ratio $\lambda = k_{\text{fast}}/k_{\text{slow}}$ as low as 10, the systems perform well.

4.5.3 FFT

For our FFT design, we the set initial concentration of S'_0 to 50nM and that of R to 100nM. Recall that S'_0 is transferred to S_0 in the first red phase and S_0 is transferred to S'_1 in first blue phase. So the computation begins with S'_1 . We set the initial concentrations of all the other types to 0. We inject I_1 and I_2 in the red phase. The output types O_1 and O_2 are produced in clock cycle 3, in a blue phase. We clear them out in following red phase. We set $k_{\text{fast}} = 10 \times k_{slow}$; and k_{slow} to 1.

The transient results of the direct implementation are shown in Figure 4.13 through Figure 4.16. The inputs are a sequence of real numbers {2.5, 3.75, 2.5, 0}.



Figure 4.12: Transient simulation result of the biquad filter.

The transient results of the parallel implementation are shown in Figure 4.17 and Figure 4.18. The inputs are a sequence of real numbers {16, 24, 16, 0}. The outputs are {56, -24j, 8, 24j}, as shown in the figures.

4.6 Remarks

This chapter presents a robust, rate-independent methodology for synchronous computation. Here "rate-independent" refers to the fact that, within a broad range of values for the kinetic constants, the computation is independent of the specific rates. The results in this chapter are complementary to prior results on *self-timed* methodologies for molecular computation in Chapter 3. As in electronic circuit design, there are advantages and disadvantages to asynchronous and synchronous design styles for molecular computing. On the one hand, a synchronous style leads to simpler designs with fewer reactions. On the other hand, errors can accumulate across clock cycles.



Figure 4.13: Transient simulation of the direct FFT output O_1 .



Figure 4.14: Transient simulation of the direct FFT output O_2 .

DNA strand-displacement reactions can emulate chemical reactions with nearly any rate structure [4]. Reaction rates are controlled by designing sequences with different binding strengths. The binding strengths are controlled by the length and sequence composition of "toehold" sequences. With the right choice of toehold sequences, reaction rates differing by as much as 10^6 can be achieved. Our contribution can be positioned as the "front-end" of the design flow – analogous to technology-independent design. DNA assembly can be considered the "back-end" – analogous to technology mapping to a specific library.



Figure 4.15: Transient simulation of the direct FFT output O_3 .



Figure 4.16: Transient simulation of the direct FFT output O_4 .

4.6.1 Comparison of RGB and Synchronous Methods

In this section, we compare the RGB method with the synchronous method. In the RGB scheme, each delay element is associated with three molecular species, whereas there are two species associated with delay elements in the synchronous scheme. However, the synchronous has a higher constant overhead due to the global clock. Therefore, for implementation overheads in terms of number of reactants and number of reactions, the synchronous method is better for systems with more delay elements. The RGB scheme is better for small-size systems.



Figure 4.17: Transient simulation of the two-parallel FFT output O_1 .

Some comparisons are listed in Table 4.1.

System	RGB		Synchronous	
	# reactants	# reactions	# reactants	# reactions
FIR filter	16	24	22	29
IIR filter	32	46	37	44
FFT(Direct)			92	88
FFT(Parallel)			72	120

Table 4.1: Comparison of RGB and Synchronous Methods.

Table 4.1 also shows that direct implementation of FFT unit use more molecular species, but with fewer reactions. This is because the parallel implementation reuses molecular species with folding. While reducing the number of reactants, folding introduces more reactions because of switch implementation.



Figure 4.18: Transient simulation of the two-parallel FFT output O_2 .

Chapter 5

The Asynchronous Scheme

In Chapter 4, we presented a fully synchronous methodology for implementing sequential computation with molecular reactions. We used a global clock, implemented through sustained chemical oscillations, to synchronize all operations. In chapter, we present a fully asynchronous methodology for molecular computation, without any global clocking mechanism.

This chapter is organized as follows. First, in Section 5.1, we present our computational model of molecular systems and we discuss how to control and transfer signals with molecular reactions. In Section 5.2, we propose a new asynchronous methodology for implementing DSP systems with molecular reactions. In Section 5.3, we present a general system synthesis flow. In Section 5.4, we provide simulation results. Finally, in Section 5.5, we give concluding remarks.

5.1 Signal Transfer Preliminaries

Sequential computation, such as DSP operations, are often modeled as data flow graphs, consisting of signal transfers through delay elements. In addition to such signal transfers there are computational elements, such as scalar multiplication and addition.

5.1.1 Signal Transfer Model

A block diagram of a general *n*-tap finite impulse response (FIR) filter is shown in Figure 5.1. A data flow graph (DFG) derived from the block diagram is shown in Figure 5.2. Each delay element in Figure 5.1 corresponds to a node in the DFG in Figure 5.2. The communicating edges in Figure 5.2 represent computation paths. The input node is marked as node X and the output node is marked as node Y. The nodes X and Y may be interpreted as input and output flip-flops.



Figure 5.1: Block diagram of a general FIR filter.



Figure 5.2: DFG of an *n*-tap FIR filter.

To implement signal transfers with molecular reactions, each node is assigned to a different molecular type. The molecular transfer from a source type to a destination type corresponding to an edge implements the signal transfer. For example, reaction

$$W_1 \longrightarrow W_2$$
 (5.1)

implements the transfer from W_1 to W_2 .

When the transfer is complete, the concentration of the destination molecular type has been increased by an amount equal to the prior concentration of source type. The concentration of the source drops to zero; when it drops to zero, the source is ready to accept a new signal value.

5.1.2 Computational Elements

Scalar multiplication

$$y = \frac{c_2}{c_1}x$$

is implemented by reaction

$$c_1 X \longrightarrow c_2 Y,$$
 (5.2)

where c_1 and c_2 are constants.

Every time this reaction fires, c_1 molecules of X get transferred to c_2 molecules of Y. Once the reaction has fired to completion, i.e., fully consumed all molecules of X, the requisite operation of scalar multiplication is complete.

Addition operation

$$y = x_1 + x_2$$

is implemented by choosing several reactions with the same product:

$$\begin{array}{rccc} X_1 & \longrightarrow & Y \\ X_2 & \longrightarrow & Y. \end{array} \tag{5.3}$$

Once both reactions have fired to completion, the concentration of Y will be the former concentration of X_1 plus the former concentration of X_2 .

The fanout operation duplicates concentrations. It is implemented by choosing a reaction producing several different products:

$$X \longrightarrow Y_1 + Y_2. \tag{5.4}$$

Once this reaction has fired to completion, both the concentration of Y_1 and the concentration of Y_2 will be equal to the former concentration of X.

In our designs, the reactions in multiplication and fanout are *fast* and reactions in signal transfer are *slow*; accordingly the computational reactions do not affect the signal transfers.

5.1.3 Absence Indication

Suppose that we have a set of molecular types $\{S_1, S_2, \dots, S_n\}$. For this set, the corresponding *absence indicator* a_S is a molecular type whose concentration is nearly zero when the concentration of any of the molecules of any type in the set is not zero; otherwise, when the concentrations of S_i $(i = 1, \dots, n)$ are all zero, the concentration of a_S is nonzero. Therefore, a_S is present in the absence of all the types. This behavior is achieved by the following reactions [16]:

Here the symbol \varnothing indicates "no reactants" meaning that the products are generated from a large or replenishable source. The first reaction slowly but continually generates molecules of a_S . In the subsequent reactions, S_1, S_2, \dots, S_n quickly consume a_S , by transferring it to a waste type we no longer track, but maintain their concentrations. Therefore, molecules of a_S accumulate only when all types in S_1, S_2, \dots, S_n are absent. Absence indication is used to control signal transfers, as discussed in the following sections.

5.2 System Implementation

In this section, we present a fully asynchronously methodology for implementing DSP systems.

5.2.1 Signal Transfer Scheduling

For fully asynchronously implementations, each directed edge of the DFG is assigned to a *step number*; it indicates the step at which the signal transfer represented by the edge takes place. This gives rise to an interesting scheduling program: how to produce an assignment of step numbers to the edges that is *conflict-free*, consisting of the fewest possible steps. We present the requirements for conflict-free signal transfer scheduling.

As discussed in Section 5.1.2, a fanout operation is implemented by a single reaction with multiple products. Therefore, all output edges of a node are assigned to the same step number:

Requirement 1

For any node V with multiple outgoing edges, $e_{o,1}, e_{o,2}, \cdots, e_{o,k}$,

$$step(e_{o,1}) = step(e_{o,2}) = \cdots = step(e_{o,k}).$$

Each node in the DFG represents a delay element. At the beginning of a computation cycle, all nodes are occupied – each with a molecular concentration reflecting the signal value it received in previous computation cycle. A node can take new signal value only after it has transferred all of its molecules to succeeding node(s). Therefore, we have:

Requirement 2

For any node V with incoming edge(s) $e_{i,1}, e_{i,2}, \cdots, e_{i,k}$ and an outgoing edge e_o ,

$$step(e_o) < min(step(e_{i,j})), j = 1, 2, \cdots k.$$

We call a node that has transferred all its molecules to succeeding node(s) an *empty* node.

An outgoing edge of node Y represents the system output of the previous cycle. It does not depend on any operation in current computational cycle. Therefore, it is always assigned to step 1:

Requirement 3

For system output Y with outgoing edge e_o ,

$$step(e_o) = 1.$$

Given these rules, we can adopt a scheduling method that assigns step numbers in increasing order from right to left on an acyclic DFG. Consider a 3-tap filter with all multiplier coefficients assigned to 1. The DFG with assigned steps for such a filter is shown in Figure 5.3. A more detailed synthesis algorithm is presented in Section 5.3.



Figure 5.3: DFG of a 3-tap FIR filter with signal transfer scheduling. Step numbers are in circles.

5.2.2 Feedback Loops

The scheduling rules discussed in Section 5.2.1 work only for acyclic DFGs, i.e., systems without feedback. For systems with feedback loops, such as infinite impulse response (IIR) filters, Requirement 2 will result in deadlock: every node in a feedback

path will wait for its succeeding node to be emptied and no one is able to proceed. Alternate scheduling methods will be needed to mitigate against this.



Figure 5.4: Block diagram of a 1-pole filter.



Figure 5.5: DFG of the 1-pole IIR filter.

A simple one-pole IIR filter and its DFG are shown in Figure 5.4 and Figure 5.5, respectively. In Figure 5.5, there is an edge both starting from and going to node W, which denotes the delay element. The technique described above cannot schedule the edge; W waits forever for itself to be emptied.

To resolve this deadlock, we break the loop by adding a temporary node T as the succeeding node of W and mark T as empty. With the loop broken and T is empty, the

scheduling technique for acyclic DFGs can be applied. Finally, the edge from T back to W needs to be added. Since T is initially empty, its outgoing edge should be assigned a step number greater than that of its incoming edge, so as to ensure that previous value of W has been fully transferred to T before it is further transferred.

Requirement 4

For any node T initially marked as empty, if its incoming edges are $e_{i,1}, e_{i,2}, \cdots, e_{i,k}$ and outgoing edge is e_o , then

$$step(e_o) > max(step(e_{i,j})), j = 1, 2, \cdots k.$$

The DGF for the IIR filter with step scheduling is shown in Figure 5.6.



Figure 5.6: DFG of the 1-pole IIR filter with signal transfer scheduling. Step numbers are in circles. Node T is denoted by a hallow cycle, which means it is empty at the beginning of a computation cycle. The newly added edge is denoted by a dashed line.

5.2.3 Mapping Signal Transfer to Reactions

With all edges in a DFG assigned with step numbers, we map the DFG to molecular reactions.

Transfer assigned to step i can fire only after all transfers assigned to step i-1 have been completed. Given a DFG with a step assignment, every node is represented by a specific molecular type. Each directed edge is mapped to a reaction transferring its source type to its destination type.

We use absence indicator type a_i to represent the completion of step i. Note that a_i is maintained by source nodes of all directed edges assigned to step i. For example, if transfers $src_1 \longrightarrow dest_1$ and $src_2 \longrightarrow dest_2$ are both assigned to step 1, then a_1 is controlled by reactions

Molecules of a_1 accumulate only when both src_1 and src_2 are absent, thus indicating that step 1 has completed.

Given the absence indicators, signal transfers of each step are enabled by the absence indicator of its previous step, except for step 1. For any directed edge e_k assigned to step *i*, the signal transfer is enabled by a_{i-1} , implemented by:

$$a_{i-1} + src(e_k) \xrightarrow{k_{slow}} dest(e_k), \quad i > 1.$$
 (5.7)

5.2.4 Conflict Elimination

Reactions (5.7) implement the signal transfers of all edges in the DFG. However, conflicts exist in this implementation. Suppose we have a signal path as shown in Figure 5.7. There are two edges in this graph, e_1 , assigned to step 2, and e_2 , assigned to step 1. These are implemented by signal transfer reactions:

and absence indication reaction:
Here, node B is both the source of a transfer in step 1 and the destination of a transfer in step 2. When step 1 is complete, all molecules of B have been transferred to C and absence indicator a_1 starts to accumulate. With a_1 , A starts to be transferred to B, which removes a_1 and further inhibits the transfer of edge e_1 . Reaction $A + a_1 \stackrel{k_{slow}}{\longrightarrow} B$ stops before A is fully transferred to B. This example shows that when a signal node is both the source of a transfer in step i and the destination of a transfer in step i + 1, the system halts.



Figure 5.7: Successive transfers.



Figure 5.8: Modified transfers.

To resolve this problem, following rule is required:

Requirement 5

$$step(e_1) \neq step(e_2) + 1$$

when

$$dest(e_1) = src(e_2).$$

To achieve this, we split each node with a conflict to two nodes. Here, B is replaced by B and B'. Initially, the value of B is represented by molecules of B' and the node B is empty. Molecules of B' are transferred to C in step 1 and Molecules of A are still transferred to B in step 2. We add another transfer, B to B', in step 3, following the transfer of A to B. The modified transfers are shown in Figure 5.8. Now there are no conflicting edges and absence indicators. Formally, when a signal node W is both the source of a transfer in step i and the destination of a transfer in step i + 1, i.e., when Requirement 5 does not hold, split W to W and W'. Add a new transfer of W to W' and assigned it with a step number one greater than the maximum step number of all incoming edges of W. Modify the reactions managing absence indicators in accordance with this change.

5.2.5 Examples



Figure 5.9: The 3-tap FIR filter modified.



Figure 5.10: The 1-pole IIR filter modified.

With conflict elimination, the DFG of the 3-tap filter is redrawn in Figure 5.9. The filter is implemented by following reactions.

Signal transfer:

$$W_{2}' + a1 \xrightarrow{k_{slow}} Y$$

$$W_{1}' + a_{2} \xrightarrow{k_{slow}} W_{2} + Y$$

$$X + a_{3} \xrightarrow{k_{slow}} W_{1} + Y$$

$$W_{2} + a_{3} \xrightarrow{k_{slow}} W_{2}'$$

$$W_{1} + a_{4} \xrightarrow{k_{slow}} W_{1}'$$

$$Y + a_{4} \xrightarrow{k_{slow}} Y'$$

To make the signal transfers robust, we also include positive feedback kinetics [35, 16]:

$$\begin{array}{ccccc} W_2' + Y & \stackrel{\mathbf{k}_{\mathrm{slow}}}{\longrightarrow} & 2Y \\ W_1' + W_2 & \stackrel{\mathbf{k}_{\mathrm{slow}}}{\longrightarrow} & 2W_2 + Y \\ X + W_1 & \stackrel{\mathbf{k}_{\mathrm{slow}}}{\longrightarrow} & 2W_1 + Y \\ \end{array}$$

$$\begin{array}{ccccc} W_2 + W_2' & \stackrel{\mathbf{k}_{\mathrm{slow}}}{\longrightarrow} & 2W_2' \\ W_1 + W_1' & \stackrel{\mathbf{k}_{\mathrm{slow}}}{\longrightarrow} & 2W_1' \\ Y + Y' & \stackrel{\mathbf{k}_{\mathrm{slow}}}{\longrightarrow} & 2Y' \end{array}$$

Absence indicator:

The DFG of the 1-pole IIR filter is redrawn in Figure 5.10. The filter is implemented by following reactions.

Signal transfer:

$$W' + a1 \xrightarrow{k_{slow}} W''$$

$$X + a_2 \xrightarrow{k_{slow}} Y + W$$

$$T + a_2 \xrightarrow{k_{slow}} W$$

$$Y + a_3 \xrightarrow{k_{slow}} Y'$$

$$W + a_3 \xrightarrow{k_{slow}} W'$$

$$2W'' \xrightarrow{k_{fast}} T + Y$$

Here, W'' is a temporary molecular type used to implement multiplication. Molecules of W'' are quickly turned to molecules of T and molecules of Y. W' does not hold any concentrations across steps. Therefore, there is no node W'' in the DFG.

Positive feedback kinetics:

$$W' + Y \xrightarrow{k_{slow}} W'' + Y$$

$$Y + Y' \xrightarrow{k_{slow}} 2Y'$$

$$W + W' \xrightarrow{k_{slow}} 2W'$$

$$X + W \xrightarrow{k_{slow}} 2W + Y$$

$$T + W \xrightarrow{k_{slow}} 2W$$

Absence indicator:

$$\begin{array}{ccc} \varnothing & \stackrel{\mathbf{k}_{\mathrm{slow}}}{\longrightarrow} & a_3 \\ X + a_3 & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & X \\ T + a_3 & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & T \end{array}$$

5.3 Synthesis Flow

We present guidelines for a full synthesis flow. The DSP system is represented by a DFG G(V, E), where the node set V represents delay elements and the edge set E represents signal transfers. Each node V_i is assigned a molecular type. The concentration of this type represents the signal stored at V_i . Each node can have three states: *full*, *processed*, and *emptied*. The scheduled procedure is as follows:

- 1. Mark all nodes as full.
- 2. Assign the outgoing edge from the system output Y to step 1. Mark Y as processed. Set current step number s = 1.
- 3. Break each loop at the point where it joins back to the graph. Add a temporary node T_i at the end of the broken loop and mark T_i as emptied.
- 4. For each source node with unscheduled fanout edges, if the destination nodes of all its fanout edges are marked as emptied, set the step numbers of all these edges to s. Mark the source node as processed.
- 5. If no more edges can be assigned to step number s, set s = s+1, mark all processed nodes as emptied, and go to 4. Repeat until all edges are assigned a step number.
- 6. For each node V_i, if there is an incoming edge e_i and an outgoing edge e_o satisfying step(e_i) = s_i = step(e_o) + 1, split V_i to V_i and V'_i. Connect all incoming edges to the new V_i and all outgoing edges to V'_i. Add a new edge from V_i to V'_i; assign it with a step number one greater than the maximum step number of all incoming edges of V_i..

- 7. With all edges assigned to non-conflicting step numbers, generate reactions for each edge according to the template of Reactions (5.7).
- 8. Finally, include the absence indicator reaction set (5.6).

5.4 Simulations

To validate our designs for the FIR and IIR filters, we map the reactions presented in Section 5.2.5 to DNA strand-displacement reactions, using the method in [4]. We generate the corresponding kinetic differential equations and simulate them. We use parameters similar to [4] ($C_{\text{max}} = 10 \mu M$, $q_{\text{max}} = 10^6 M^{-1} s^{-1}$). The reaction constant for the "slow" reactions is set to $k_{\text{slow}} = 5.56 \times 10^4 M^{-1} s^{-1}$. For "fast" reactions it is set to $k_{\text{fast}} = 3 \times k_{\text{slow}}$.



Figure 5.11: Simulation results of the FIR filter.

The simulation results for DNA-level designs of the two filters are shown in Figure 5.11 and Figure 5.12. The input is a time-varying signal concentration X with



Figure 5.12: Simulation results of the IIR filter.

both high-frequency and low-frequency components. The outputs are time-varying signal concentrations Y'. Molecules of X are injected and molecules of Y' are collected from the system every 25 hours. The figure shows the theoretical output, i.e., an exact calculation of filtering, as well as simulation results.

We see that our design performs very well. The simulated output matches the theoretical output. The small errors are caused by leakage among molecular types. The average relative error for the FIR filter is 7.65%. For the IIR filter, it is 12.69%. Although the FIR filter has one more delay element and more molecular types and signal transfers, it has a lower error than the IIR filter. Generally, IIR filters have higher errors than FIR filters, since feedback in such filters leads to error accumulation.

5.5 Remarks

This chapter presents a robust, rate-independent methodology for asynchronous computation with molecular reactions. Here "rate-independent" refers to the fact that,

within a broad range of values for the kinetic constants, the computation is exact and independent of the specific rates.

The results in this chapter are complementary to prior work on a synchronous methodology for molecular computation [16]. As in electronic circuit design, there are advantages and disadvantages to asynchronous and synchronous design styles for molecular computing. The synchronous methodology leads to simpler designs but with more reactions. In [16], each delay is represented by three molecular types and the computation completes in three steps. In the asynchronous methodology proposed in this chapter, each delay is represented by no more than two molecular types; however, the number of steps is linear in the number of delay elements.

The methodology in this chapter was presented at a conceptual level in terms of abstract molecular types. All the designs were mapped to DNA-strand displacement reactions; the simulation results that we presented were for DNA-level designs. Such designs can readily be implemented *in vitro*.

Indeed, a group at Caltech has shown that DNA reactions can emulate the chemical kinetics of nearly any chemical reaction network. They also provide a compiler that translates abstract chemical reactions of the sort that we design into specific DNA reactions [4]. Recent work has demonstrated both the scale of computation that is possible with DNA-based computing [38], as well as exciting applications [23]. While conceptual, our work suggest a *de novo* approach to the design of biological functions. Potentially this approach is more general in its applicability than methods based on appropriating and reusing existing biological modules. This could lead to novel *in vivo* applications.

Chapter 6

Implementing Sequential Logic

There has been a groundswell of interest in molecular computation in recent years [39, 40, 41, 42, 3, 43, 38, 44, 45, 46, 47, 9, 16]. In prior work, computations are implemented with particular molecular systems such as gene transcription networks and deoxyribozyme. These provide a bottom-up way to build complex circuits. In particular, there have been several attempts to apply concepts from digital circuit theory to biological engineering. Numerous types of genetic gates have been proposed [25, 48, 49, 50, 26, 28, 29, 51]. Cascaded digital circuits implemented with abstract chemical reactions have been published [52]. Also, dating back to seminal work by Kauffman, gene networks are often modeled as directed graphs in which there is an arrow from one node to another if and only if there is a causal link between the corresponding genes; the node itself is viewed as a Boolean function of its inputs; its state is either "on" or "off" depending on the level of gene expression [53]. These are all based on combinational digital logic. Although biochemistry-based automata [54] and latches based on cross-coupled combinational logic [4] have been proposed, there have not yet been methods that implement full-scale sequential digital logic.

Here we propose a novel methodology for systematic synthesis of sequential digital logic with molecular reactions. Given a digital logic system, our method generates a chemical reaction network (CRN) that performs the exact functionality of the system. The generated CRN is ready to be mapped to DNA strand displacement [4] – all reactions are bimolecular and there are only two rate constants, i.e., k and k_{slow} . Specific values of the constants do not affect computation accuracy – as long as k is greater than k_{slow} , the computations are exact. We represent each digital bit with a form of "dual-rail" encoding [55]: the value of a bit is not determined by the concentration of a single molecular type. Rather, it is the comparison of the concentrations of two complementary types that determines if the bit is "0" or "1". This mechanism is robust: any small amount of perturbation or leakage in the concentrations quickly gets cleared out and the signal value is not affected. Based on this bit representation, we present designs for combinational components – AND, OR, and XOR. Unlike previous work focusing on logic gates, we also design sequential components – D latches and D flip-flops, with which sequential digital circuit functions can be performed. Our method shows implementation of large-scale sequential logic with DNA strand displacement is possible.

This chapter is organized as follows. In Section 6.1, we provide an overview of prior work. In Section 6.2, we describe the bistable mechanism for representing binary bits. In Section 6.3, we discuss the implementation of logic gates. In Section 6.4, we discuss the implementation of D latches and D flip-flops. In Section 6.5, we present the examples of a square-root unit, a binary counter and a linear feedback shift register. Finally, in Section 6.6, we discuss potential applications of our design methodology.

6.1 Related Work

Hjelmfelt et al presented a chemical implementation of McCullock-Pitts neurons [56]. A bistable mechanism is implemented by four reversible reactions. State of each neuron is determined by concentrations of excitation species of the neuron. Logic gates such as AND and NOR are implemented based on M-P neurons. They further extended this work to chemical implementation of finite-state machines [57]. In our work, we also use bistable mechanism for signal representation. However, our mechanism is much simpler: only three non-reversible reactions are required for each bit signal. In addition, unlike in [56] and [57], functions of logic gates in our work do not depend on initial concentrations of certain species, which are inaccuracy-prone. Rather, whether a gate is AND or OR is coded in the system design phase; it does not change with detailed implementation.

Qian et al demonstrated several digital logic circuits based on a simple DNA gate motif which is called a "seesaw gate" [9]. Unlike our work, circuits built with seesaw gate are combinational, not sequential. Furthermore, our gates can perform more than once because there is no requirement for preset threshold species, which are destroyed after each execution of the gates.

In [4], Soloveichik et al presented a flip-flop based on cross-coupled NOR gates, and further demonstrated it though a pulse counter. Our flip-flop does not use crosscoupled gates to lock signal values. Instead, bit signals are locked by the much simpler bi-stability reactions. Due to the simplicity of the bit reactions, our work implements more complex systems with fewer reactions and DNA strands.

6.2 Bit Representation

The most straightforward interpretation of binary values in the context of molecular computation is to assign a threshold to the concentration of a designated molecular type [58, 59]. When the concentration exceeds a threshold level, the bit is considered a logical 1; otherwise it is consider a logical 0. Although such a representation is conceptually simple, it requires external mechanisms for comparing the concentration of the designated molecular type with the threshold. Furthermore, it suffers from signal degradation over time: unwanted residue accumulates every time a signal is changed, unless there is some mechanism to clear the signal. To mitigate these issues, we use a complementary representation (reminiscent of a "dual-rail" encoding). For a single bit X, we use two molecular types, X_0 and X_1 . The presence of X_0 indicates that X is set to 0; the presence of X_1 indicates that X is set to 1. Clearly, X_0 and X_1 should not be present at the same time or else the value of X would be ambiguous. We use following set of reactions to ensure that this does not happen:

In these reactions, a molecule of X_0 combines with a molecule of X_1 to produce a molecule of S_X . This molecule of S_X then combines with a molecule of X_0 or one of X_1 , depending on which it meets first. The choice is competitive: both X_0 and X_1 are trying to increase their concentration via the intermediary type S_X ; whichever has a higher concentration wins. The concentration of the loser drops to zero. So this mechanism clears out the leakage of molecular types that would otherwise occur when bits are set. Signal transfer diagram of a binary bit is shown in Figure 6.1.



Figure 6.1: Signal transfer diagrams of a binary bit. In the diagram, solid-line arrows denote "transfers to" and dashed-line arrows denote "enables".

To further elucidate the behavior of Reactions 6.1, consider their kinetic equations:

$$\begin{aligned} \frac{d[S_X]}{dt} &= k[X_0][X_1] - k[S_X][X_0] - k[S_X][X_1] \\ \frac{d[X_0]}{dt} &= -k[X_0][X_1] + 2k[S_X][X_0] \\ \frac{d[X_1]}{dt} &= -k[X_0][X_1] + 2k[S_X][X_1]. \end{aligned}$$

Suppose the combined initial concentration of X_0 and X_1 is C and that the initial concentrations of S_X is 0. There are three steady-state solutions: $\{[X_0] = 2C/5, [X_1] = 2C/5\}$, $\{[X_0] = 0, [X_1] = C\}$, and $\{[X_0] = C, [X_1] = 0\}$. The first is unstable. It is a saddle point: any small perturbation leads to one of the other two solutions, which are both stable. This bistability forms the basis of our representation of a bit.

Note that the specific values of k do not affect the behavior of the bit mechanism; the ratio is always 1. In physical implementation, as long as the rate constants in Reactions 6.1 are within same range, the robust bistable mechanism of bits holds.

6.3 Implementing Combinational Logic Gates

Given the robust representation of binary bits, here we demonstrate logic gates can be implemented with molecular reactions. We only consider two-input gates; gates with more than two inputs can be easily implemented by cascading two-input gates.

Suppose the inputs of a gate are X and Y, and the output is Z. These signals are represented by the concentrations of X_0/X_1 , Y_0/Y_1 , and Z_0/Z_1 , respectively. Each one of X, Y, and Z is regulated by its own version of the bistable bit reactions. For each of the four entries in the truth table for the gate, if the value of Z is 1, then molecules of Z_0 , if any, should be transferred to Z_1 . Similarly, if the value of Z is 0, then molecules of Z_1 , if any, should be transferred to Z_0 .

6.3.1 AND Gate and OR Gate

Let us first consider an AND gate. By definition, either X = 0 or Y = 0 sets Z to 0, which means that when either X_0 or Y_0 is present, Z_0 should be generated and Z_1 should be cleared out. This is implemented by the reactions

$$\begin{array}{cccc} X_0 + Z_1 & \stackrel{k}{\longrightarrow} & X_0 + Z_0 \\ Y_0 + Z_1 & \stackrel{k}{\longrightarrow} & Y_0 + Z_0. \end{array}$$

$$\tag{6.2}$$

Here, X_0 and Y_0 transfer Z_1 to Z_0 but keep their own concentrations unchanged. Z is set to 0 if it has not already been.

Z should be set to 1 only when both X = 1 and Y = 1. This is implemented by the reactions

$$X_{1} + Y_{1} \xrightarrow{k} X_{1} + Y_{1} + Z'_{1}$$

$$2Z'_{1} \xrightarrow{k} \varnothing$$

$$Z'_{1} + Z_{0} \xrightarrow{k} Z_{1}.$$
(6.3)

In the first reaction, X_1 combines with Y_1 to generate Z'_1 , an indicator that Z should be set to 1. The concentrations of X_1 and Y_1 do not change. Z'_1 is transferred to an external sink, denoted by \emptyset , in the second reaction. (This could be a waste type whose concentration we do not track.) When molecules of both X_1 and Y_1 are present, these reactions maintain the concentration of Z'_1 at an equilibrium level $[Z'_1] = \sqrt{[X_1][Y_1]} = C$. When one of X_1 and Y_1 is not present, Z'_1 gets cleared out. In the last reaction, Z'_1 transfers Z_0 to Z_1 . Taken together, bistable bit reactions, Reactions 6.2 and 6.3 implement an AND gate. Signal transfer diagram of the AND gate is shown in Figure 6.2(a).

The reactions for the OR gate are similar to those for the AND gate. Either X = 1or Y = 1 sets Z to 1. This entails having both X_1 and Y_1 transfer Z_0 to Z_1 :

$$\begin{array}{cccc} X_1 + Z_0 & \xrightarrow{\mathbf{k}} & X_1 + Z_1 \\ Y_1 + Z_0 & \xrightarrow{\mathbf{k}} & Y_1 + Z_1. \end{array} \tag{6.4}$$

When both X = 0 and Y = 0, molecules of Z_1 are transferred to Z_0 :

$$\begin{array}{ccccc} X_0 + Y_0 & \stackrel{k}{\longrightarrow} & X_0 + Y_0 + Z'_0 \\ & & 2Z'_0 & \stackrel{k}{\longrightarrow} & \varnothing \\ & & & Z'_0 + Z_1 & \stackrel{k}{\longrightarrow} & Z_0. \end{array}$$

$$(6.5)$$

NAND gate and NOR gate can be implemented by effecting the transfers between Z_0 and Z_1 in the opposite directions of those of the AND and OR gates. We illustrate for the NOR gate only. Together with bistable bit reactions, the following reactions implement the NOR gate:

6.3.2 XOR gate

We could, of course, implement an exclusive-OR (XOR) gate with say NAND gates or NOR gates. Instead, we present a direct implementation. For XOR gate, Z = 1when $X \neq Y$. Therefore, molecules of Z_0 are transferred to Z_1 when both X_0 and Y_1 are present, or when both X_1 and Y_0 are present:

Similarly, when both X_0 and Y_0 are present, or when both X_1 and Y_1 are present, molecules of Z_1 are transferred to Z_0 :

Signal transfer diagram of XOR gate is shown in Figure 6.2(b).



Figure 6.2: Signal transfer diagrams of (a) AND gate. (b) XOR gate. Square boxes with "S" denote external sources to generate certain molecular types. \emptyset denotes external sinks, which are waste type we do not track.

To obtain the input/output behaviors of the gates, we map the chemical reactions to DNA strand displacement reactions and solve the kinetics of the DNA strands. Results are shown in Figure 6.3. In this figure, input signals are X and Y; output signal is Z. Chemical reactions are mapped to DNA strand displacement reactions in accordance

with [4]. Maximum strand displacement rate constant $q_{max} = 10^6 M^{-1} s^{-1}$; initial concentration of auxiliary species $C_{max} = 10\mu M$. The initial concentrations are set as: $[Z_1] = [Z'_1] = [Z'_0] = 0$, and $[S_X] = [S_Y] = [S_Z] = 0$. Note that $[Z_0]$ can be set to any nonzero value C; we used C = 10nM in this simulation. We sweep the range of initial values of $[X_1]$ and $[Y_1]$ from 0 to C; correspondingly, we sweep X_0 and Y_0 from C to 0. The resulting values of Z_1 for each input combination are recorded after 20 hours of reaction time. Normalized values are shown in each figures. Because bistable bit reactions apply for all signals, all four gates shows clean and stiff cutoff behavior at threshold values of input signals.



Figure 6.3: Input/Output behavior of logic gates. (a) AND gate. (b) OR gate. (c) NOR gate. (d) XOR gate.

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6.3.3 Multiplexer

A multiplexer selects one of two data inputs A and B and forwards the input's value to its output Z, based on the value of the select input S. Z = A when S = 0; Z = Bwhen S = 1.

Multiplexer can be implemented as $Z = A\overline{S} + BS$, by two AND gates and one OR gate. However, here we present a simpler way to implement multiplexer:

$$S_{0} + A_{0} \stackrel{k}{\longrightarrow} S_{0} + A_{0} + A'_{0}$$

$$2A'_{0} \stackrel{k}{\longrightarrow} \varnothing$$

$$S_{0} + A_{1} \stackrel{k}{\longrightarrow} S_{0} + A_{1} + A'_{1}$$

$$2A'_{1} \stackrel{k}{\longrightarrow} \varnothing$$

$$S_{1} + B_{0} \stackrel{k}{\longrightarrow} S_{1} + B_{0} + B'_{0}$$

$$2B'_{0} \stackrel{k}{\longrightarrow} \varnothing$$

$$S_{1} + B_{1} \stackrel{k}{\longrightarrow} S_{1} + B_{1} + B'_{1}$$

$$2B'_{1} \stackrel{k}{\longrightarrow} \varnothing$$

$$A'_{0} + A_{1} \stackrel{k}{\longrightarrow} A_{0}$$

$$A'_{1} + A_{0} \stackrel{k}{\longrightarrow} A_{1}$$

$$B'_{0} + B_{1} \stackrel{k}{\longrightarrow} B_{1}.$$
(6.9)

In Reactions 6.9, value of Z is directly control by A or B, based on the value of S.

6.3.4 Kinetic Analysis

Bistable bit reactions strive to retain the previous value of Z. However, when the inputs of a gate change and molecules of one of Z_0 or Z_1 are transferred to the other, the "force" to keep the previous value set by bistable bit reactions is overcome by the "force" changing it.

Consider an AND gate with initial concentrations $Z_0 = 0$ and $Z_1 = C$, and the following reaction resetting Z to 0:

$$X_0 + Z_1 \xrightarrow{k} Z_0 + X_0. \tag{6.10}$$

Here, concentration of X_0 is $[X_0] = C$. Considering bistable reactions for Z

$$Z_0 + Z_1 \xrightarrow{k} S_Z$$
$$S_Z + Z_0 \xrightarrow{k} 3Z_0$$
$$S_Z + Z_1 \xrightarrow{k} 3Z_1,$$

rate of change of Z_0 is

$$\frac{d[Z_0]}{dt} = -k[Z_0][Z_1] + 2k[S_Z][Z_0] + k[X_0][Z_1]$$
$$= -k[Z_0][Z_1] + 2k[S_Z][Z_0] + kC[Z_1].$$

Since $[Z_0] \leq C$, $kC[Z_1] > k[Z_0][Z_1]$, $d[Z_0]/dt > 0$, and Z_1 is continually transferred to Z_0 until finished.

Similar results can be obtained for other gates and cases that set Z to 1.

6.4 Implementing Sequential Logic

6.4.1 Clock

Sequential operations require a clock with alternating phases. There have been considerable progress towards synthesizing *in vitro* biochemical oscillators [60, 61, 62]. In this work, we use the clock presented in [17], which is a 4-phase oscillator based on molecular transfer gates.

The clock phases are represented by molecular types R(ed), G(reen), B(lue), and V(iolet). First consider the reactions:

Ø	$\stackrel{k_{slow}}{\longrightarrow}$	r		R+r	$\stackrel{k}{\longrightarrow}$	R
Ø	$\stackrel{k_{\rm slow}}{\longrightarrow}$	g	and	G+g	$\stackrel{k}{\longrightarrow}$	G
Ø	$\stackrel{k_{\rm slow}}{\longrightarrow}$	b		B + b	$\stackrel{k}{\longrightarrow}$	В
Ø	$\stackrel{k_{\rm slow}}{\longrightarrow}$	v		V + v	$\stackrel{k}{\longrightarrow}$	V.
		(6.11)				(6.12)

In Reactions 6.11, the molecular types r, g, b, and y are generated slowly and constantly. Here the symbol \varnothing indicates "no reactants" meaning the products are generated from a large or replenishable source. In Reactions 6.12, the types R, G, B, and Y quickly consume the types r, g, b, and y, respectively. Call R, G, B, and Y the *phase signals* and r, g, b, and y the *absence indicators*. The latter are only present in the absence of the former. The reactions

$$R + v \xrightarrow{k_{\text{slow}}} G$$

$$G + r \xrightarrow{k_{\text{slow}}} B$$

$$B + g \xrightarrow{k_{\text{slow}}} V$$

$$V + b \xrightarrow{k_{\text{slow}}} R$$

$$(6.13)$$

transfer one phase signal to another, in the absence of the previous one. The essential aspect is that, within the RGBY sequence, the full quantity of the preceding type is transfered to the current type before the transfer to the succeeding type begins.

To achieve sustained oscillation, we introduce positive feedback. This is provided by the reactions

Consider the first three reactions. Two molecules of G combine with one molecule of R to produce three molecules of G. The first step in this process is reversible: two molecules of G can combine, but in the absence of any molecules of R, the combined form will disassociate back into G. So, in the absence of R, the quantity of G will not change much. In the presence of R, the sequence of reactions will proceed, producing one molecule of G for each molecule of R that is consumed. Here, all reactions are expressly designed to have two reactants; as discussed before, this permits us to map the reactions to DNA strand displacement reactions effectively. Due to the first reaction, the transfer will occur at a rate that is super-linear in the quantity of G; this speeds up the transfer and so provides positive feedback.

Suppose that the initial quantity of R is set to some non-zero amount, and the initial quantity of the other types is set to zero. We will get an oscillation among the quantities of R, G, B, and Y. We choose two nonadjacent phases, G and V, as the clock phases.

6.4.2 D Latch

A D latch has two inputs, the latch input D and an enable signal, and one output Q (Figure 6.4(a)). V combines D_0 or D_1 to generate an equilibrium amount of Q'_0 or Q'_1 , which determine the transfer between Q_0 and Q_1 . When V is absent, Q retains its previous value. When the enable signal is 0, the latch holds the last input value that it saw when the enable signal was still 1. We could, of course, implement such a D latch with cross-coupled NOR gates, as in electronic circuits. Instead, we present a direct implementation based upon our bistable construct for binary values. Indeed, Reactions 0 provide a state-locking mechanism. Based on those reactions, we introduce an enabling signal CLK such that value of the input is transferred to output only when CLK = V. When CLK = G, the state-locking mechanism holds the output value.

The D latch is implemented by following reactions:

$$V + D_{0} \xrightarrow{k} V + D_{0} + Q'_{0}$$

$$V + D_{1} \xrightarrow{k} V + D_{1} + Q'_{1}$$

$$2Q'_{0} \xrightarrow{k} \varnothing$$

$$2Q'_{1} \xrightarrow{k} \varnothing$$

$$Q'_{0} + Q_{1} \xrightarrow{k} Q_{0}$$

$$Q'_{1} + Q_{0} \xrightarrow{k} Q_{1}.$$

$$(6.15)$$

With enabling type V is present, the first two reactions generate Q'_0 or Q'_1 , with presence of input signals D_0 or D_1 , respectively. The next two reactions ensure that molecules of Q'_0 (Q'_1) do not accumulate when there are no molecules of D_0 (D_1) in presence. Finally, the last two reactions set Q to 0 or 1, in accordance with presence of Q'_0 or Q'_1 .

6.4.3 D Flip-Flop

Unlike a latch, a flip-flop reacts to changes in its enabling signal. If the enabling signal is clock, then the flip-flop only grabs its input on the rising edge of the clock, that is to say when the clock signal changes from 0 to 1. We implement a D flip-flop with a

master-slave configuration of D latches, as shown in Figure 6.4(b). In this configuration, the signal D goes through two D latches in series. When CLK = G, the master latch is enabled and the value of D passes through it. Meanwhile, the slave latch retains its previous value. When CLK turns to V, the master latch is switched off and retains its previous value. At the same time, slave latch is enabled and the value from the master latch passes through. This mechanism is implemented by the following reactions:

$$CLK_{0} + D_{0} \stackrel{k}{\longrightarrow} CLK_{0} + D_{0} + M'_{0}$$

$$CLK_{0} + D_{1} \stackrel{k}{\longrightarrow} CLK_{0} + D_{1} + M'_{1}$$

$$2M'_{0} \stackrel{k}{\longrightarrow} \varnothing$$

$$2M'_{1} \stackrel{k}{\longrightarrow} \varnothing$$

$$M'_{0} + M_{1} \stackrel{k}{\longrightarrow} M_{0}$$

$$M'_{1} + M_{0} \stackrel{k}{\longrightarrow} M_{1}$$

$$CLK_{1} + M_{0} \stackrel{k}{\longrightarrow} CLK_{1} + M_{0} + Q'_{0}$$

$$CLK_{1} + M_{1} \stackrel{k}{\longrightarrow} CLK_{1} + M_{1} + Q'_{1}$$

$$2Q'_{0} \stackrel{k}{\longrightarrow} \varnothing$$

$$2Q'_{1} \stackrel{k}{\longrightarrow} \varnothing$$

$$Q'_{0} + Q_{1} \stackrel{k}{\longrightarrow} Q_{0}$$

$$Q'_{1} + Q_{0} \stackrel{k}{\longrightarrow} Q_{1}.$$

$$(6.16)$$

We also include the bistable bit operation reactions for M and Q. In the set of Reactions 6.16, the first six reactions implement the master latch, which is enabled by CLK_0 . The slave latch, enabled by CLK_1 , takes M_0 and M_1 , the output of the master latch, as its input signals. It is implemented by the last six reactions.

The transient simulation results are shown in Figure 6.4(c–f). Maximum strand displacement rate constant $q_{max} = 10^6 M^{-1} s^{-1}$; initial concentration of auxiliary species $C_{max} = 10 \mu M$. They are obtained by simulating DNA strand-displacement reactions mapped from Reactions 6.16. Clearly, the output Q follows the value of D only at rising edges of the CLK signal.



Figure 6.4: Sequential components: D latch and D flip-flop. (a) Signal transfer of a D latch. (b) Schematic of a D flip-flop. (c) D latch with an external perfect clock which provides square-wave phase signals. (d) D latch with oscillator described in Section 6.4.1 as input clock. We see that Q follows D only when $[CLK_1]$ is significantly large. (e) D flip-flop with perfect input clock. (f) D flip-flop with oscillator as input clock. We see that Q follows D only when $[CLK_1]$ is significantly large. (e) that Q follows D only when $[CLK_1]$ significantly increases.

6.5 Examples

We demonstrate three full-fledged examples of digital designs implemented with molecular reactions: a combinational digit-serial square-root unit, an asynchronous three-bit binary counter, and a synchronous linear feedback shift register (LFSR).

6.5.1 A Square-Root Unit

We implement a square-root unit [63] with our constructs for logic gates (The design presented here is with a 4-bit output). It consists of 14 controlled add subtract cells (CAS). a_7 is the most significant bit of input; a_0 is the least significant bit. q_3 is the most significant bit of output; q_0 is the least significant bit. There are eight gates in each CAS. Each gate is implemented by corresponding molecular reactions discussed in previous section. The unit computes square-root in a systematic way and can be easily extended to *n*-bit output, for values of n > 4.

Figure 6.5 shows the schematic and simulation results of the square-root unit. Maximum strand displacement rate constant $q_{max} = 10^6 M^{-1} s^{-1}$; initial concentration of auxiliary species $C_{max} = 10 \mu M$. In Figure 6.5(c), the input values for the system are $a_7 a_6 \cdots a_0 = 10101001$, $a_7 a_6 \cdots a_0 = 01100001$, $a_7 a_6 \cdots a_0 = 01111111$, respectively. The outputs correctly show the square root of the input values. We see that the less significant bits reach the correct levels more slowly than more significant bits, because the values of the former depend on the values of the latter.

6.5.2 A Binary Counter

We then apply our method to sequential logic circuits, as shown in Figure 6.6. An asynchronous binary counter is shown in Figure 6.6(a). It is similar to that shown in [58], but implemented with our master-slave D flip-flop. In this counter, clock is used as the input of the first stage. The circles in the figure denote inversion. However, no inversion reaction is actually required, since we can simply feed output of a stage



Figure 6.5: Examples: a square-root unit. (a) Schematic of a CAS. (b) Schematic of the unit. (c) Transient behaviors of the unit with inputs set to $a_7a_6\cdots a_0 = 10101001$, $a_7a_6\cdots a_0 = 01100001$, $a_7a_6\cdots a_0 = 01111111$, respectively.

to the opposites of its input and clock of next stage. For example, Q_0^0 is transferred to D_1^0 . Figure 6.6(b) and Figure 6.6(c) show the transient system responses with an external perfect clock and with oscillator described above as clock. Maximum strand displacement rate constant $q_{max} = 10^6 M^{-1} s^{-1}$; initial concentration of auxiliary species $C_{max} = 10 \mu M$. $k = 3k_{slow}$. With the perfect clock, the system behaves almost perfectly as a binary counter. With the oscillator, signals degrade when clock changes. However, their logic value are generally preserved.



Figure 6.6: Examples: a three-bit counter. (a) Schematic of the three-bit counter. (b–c) Transient behavior of the counter. We see that the counter counts from "000" to "111" in eight cycles. (b) Input clock is an external perfect clock which provides square-wave phase signals. (c) Input clock is the oscillator described in Section 6.4.1.

Full list of reactions implementing the counter unit is provided in Section B.1.

6.5.3 A Linear Feedback Shift Register

The third example is a three-bit LFSR (Figure 6.7). It generates pseudo-random bit strings. It contains three D flip-flops and one XOR gate. All D flip-flops are synchronized by CLK signal. Output B and C are XORed and fed back to the first flip-flop. Similar to the counter, perfect clock generates nearly perfect system behavior and using internal oscillator as clock yields degraded yet discernible output signals. Here, again, Maximum strand displacement rate constant $q_{max} = 10^6 M^{-1} s^{-1}$; initial concentration of auxiliary species $C_{max} = 10 \mu M$. $k = 3k_{slow}$.

Full list of reactions implementing the LFSR unit is provided in Section B.2.



Figure 6.7: Examples: a linear feedback shift register. (a) Schematic of the LFSR. (b–c) Transient behavior of the LFSR. We see that starting from "111", all possible values of "*ABC*", except "000", are visited. (b) Input clock is an external perfect clock which provides square-wave phase signals. (c) Input clock is the oscillator described in Section 6.4.1.

6.6 Discussion

Most prior schemes for molecular computation depend on specific values of the rate constants, which limits their applicability since the rate constants are not constant at all; they depend on factors such as cell volume and temperature. The results of the computation are not robust. We aim for robust constructs: in our methodology we require only a coarse value for the kinetic constants. Given the coarse value for these constants, the computation is exact. It does not matter how fast the reactions are – only that all reactions fire at relatively similar rates.

Our implementation of latch based on the bistable bit operation reactions is efficient – the value of a bit is secured with positive feedback kinetics within the bit. This idea leads to a much more concise design than traditional designs with cross-couple logic gates. Flip-flops presented in [4] require 60 reactions each. In contrast, each D flip-flop is implemented by 18 reactions in our work.

The system can be further optimized. Previously we assume bistable bit operation reactions are applied to every binary bit in the system. However, for some binary bits, these reactions can be removed without compromising signal integrity, especially for systems without loops. Along a signal path, bit operation reactions can be applied to one bit of every three/four bits as "signal regulators". The places to put these reactions depend on system structure, precision of reaction constants of the implementation, etc. For example, erroneous residues/leakage are more likely to accumulate in systems with loops, therefore more bistable reactions are required, possibly for every bit.

Chapter 7

Conclusions and Future Directions

7.1 Summary

This dissertation addresses the synthesis and implementation of digital signal processing operations in an entirely new application domain: *molecular computing*. In contrast to electronic systems, where signals are represented by time-varying voltage values, in molecular systems signals are represented by time-varying *quantities of different molecular types*, such as DNA. Through custom DNA synthesis, molecular systems consisting of specific types can be synthesized and manipulated. The challenge in performing molecular computation is that the chemical reactions operating on these types fire asynchronously and in parallel.

Techniques for analyzing the dynamics of biological systems are well established. However, synthesizing computation with such mechanisms requires new techniques – and an entirely new mindset. Building upon very promising results, the dissertation develops a full methodology for synthesizing robust digital logic and signal processing operations with molecular systems. The key idea underpinning the methodology is a technique for rate-independent chemical computation: a way of structuring chemical reactions such that they produce specific quantities of output types as a function of quantities of input types, regardless of the rate at which the constituent reactions fire. Synthesis first will be performed at a conceptual level, in terms of abstract biomolecular reactions – a task analogous to *technology-independent synthesis* in integrated circuit design. Then the results will be mapped onto specific biomolecular components, selected from libraries – a task analogous to *technology mapping* in integrated circuit design.

The dissertation addresses the following design challenges: transforming time-domain signals into spectral-domain signals by Fast Fourier Transform (FFT) operations; implementing general filtering operations such as high, low, and band-pass filtering; and implementing sequential digital logic. (In all cases, the inputs and outputs are timevarying quantities of molecular types. For instance, in the case of an FFT, the output is a time-varying quantity that corresponds to the frequency of the changes in the input quantity.) All designs are translated to DNA-strand displacement reactions. Potential applications include drug delivery, cancer treatment and biochemical sensing.

7.2 Future Directions

In the future, the impact of specific DSP constructs such as pipelining, retiming, folding and unfolding on biomolecular designs will be investigated. The methodology will be developed and evaluated both in a conceptual sense and in a practical sense. the proposed research will transform disciplines such as genetic engineering of drug-delivery systems. Currently, a costly, ineffective ad-hoc approach prevails. With robust and rate-independent techniques for implementing operations such as digital signal processing, much more effective systems will be developed.

A second future direction is to further optimize the systems. Numbers of reactions and number of molecular species can be further minimized at architecture level, abstract molecular level, and DNA level. An optimized system leads to better DNA implementability.

Another future direction is to physically implement the designed systems with DNA. Although the mapping of abstract molecular reactions to DNA strand displacement reactions has been demonstrated in [4], the designs we presented in this dissertation have yet been physically implemented. We expect non-idealities such as buffering effects could affect computation accuracy and sustainability of oscillation. Automatic design aids will be studied based on experimental results.

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Appendix A

List of Molecular-Level Reactions of Synchronous Systems

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A.1 Synchronous FIR filter

Clock reactions:

Blue phase signal transfer:

B + X	$\stackrel{k_{\rm slow}}{\longrightarrow}$	A + C + B
B + D	$\stackrel{k_{\rm slow}}{\longrightarrow}$	Y + B

Red phase signal transfer:

 $\begin{array}{ccc} R+D' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D+R.\\ \\ & 2A & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & D'\\ \\ & 2C & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & Y. \end{array}$

Computation:

A.2 Synchronous IIR filter

Clock reactions:

Blue phase signal transfer:

$$B + X \xrightarrow{k_{slow}} A + D'_1 + B$$
$$B + D_1 \xrightarrow{k_{slow}} F + C + D'_2 + B$$
$$B + D_2 \xrightarrow{k_{slow}} H + E + B.$$

Red phase signal transfer:

$$R + D'_1 \stackrel{k_{\text{slow}}}{\longrightarrow} D_1 + R$$
$$R + D'_2 \stackrel{k_{\text{slow}}}{\longrightarrow} D_2 + R.$$

Computation:

$$\begin{array}{ccccccc} 2A & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & A_2 \\ 2A_2 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & A_4 \\ 2A_4 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & Y \\ 2C & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & C_2 \\ 2C_2 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & C_2 \\ 2C_2 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & C_4 \\ 2C_4 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & Y \\ 2E & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & E_2 \\ 2E_2 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & E_4 \\ 2E_4 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & F_2 \\ 2F_2 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & F_4 \\ 2F_4 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & F_4 \\ 2F_4 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & H_2 \\ 2H_2 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & H_4 \\ 2H_4 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & X. \end{array}$$

A.3 FFT Unit

Clock reactions:

A.3.1 Direct Implementation

Buffers:

$$\begin{array}{cccc} R+D_{1,p}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{1,p}+R \\ R+D_{1,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{1,n}+R \\ R+D_{1,p}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{1,p}^*+R \\ R+D_{1,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{1,n}^*+R \\ R+D_{2,p}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{2,p}+R \\ R+D_{2,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{2,n}+R \\ R+D_{2,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{2,p}^*+R \\ R+D_{2,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{2,n}^*+R \\ R+D_{2,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{2,n}^*+R \\ R+D_{3,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{3,n}^*+R \\ R+D_{3,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{3,p}^*+R \\ R+D_{3,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{3,n}^*+R. \end{array}$$

Signal transfers:

A.3.2 Two-Parallel Implementation

Switch reactions:

$$B + S_1 \xrightarrow{k_{\text{slow}}} S'_0 + B$$
$$B + S_0 \xrightarrow{k_{\text{slow}}} S'_1 + B$$
$$V + S'_0 \xrightarrow{k_{\text{fast}}} S_0 + V$$
$$V + S'_1 \xrightarrow{k_{\text{fast}}} S_1 + V$$

$$\begin{array}{cccc} S_0' + S_1' & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & S' \\ S' + S_0' & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 3S_0' \\ S' + S_1' & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 3S_1' \\ S_0 + S_1 & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & S \\ S + S_0 & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 3S_0 \\ S + S_1 & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 3S_1. \end{array}$$

Blue phase signal transfer reactions:

$$\begin{split} S_{0}' + D_{4,p} & \xrightarrow{k_{\text{slow}}} & O_{1,p} + O_{2,n} + S_{0}' \\ S_{0}' + D_{4,n} & \xrightarrow{k_{\text{slow}}} & O_{1,n} + O_{2,p} + S_{0}' \\ S_{0}' + D_{4,p}^{*} & \xrightarrow{k_{\text{slow}}} & O_{1,p}^{*} + O_{2,n}^{*} + S_{0}' \\ S_{0}' + D_{4,n}^{*} & \xrightarrow{k_{\text{slow}}} & O_{1,n}^{*} + O_{2,p}^{*} + S_{0}' \\ S_{1}' + D_{4,p} & \xrightarrow{k_{\text{slow}}} & D_{3,p}' + S_{1}' \\ S_{1}' + D_{4,n} & \xrightarrow{k_{\text{slow}}} & D_{3,n}' + S_{1}' \\ S_{1}' + D_{4,p}^{*} & \xrightarrow{k_{\text{slow}}} & D_{3,p}' + S_{1}' \\ S_{1}' + D_{4,n}^{*} & \xrightarrow{k_{\text{slow}}} & D_{3,p}' + S_{1}' \\ S_{1}' + D_{4,n}^{*} & \xrightarrow{k_{\text{slow}}} & D_{3,n}' + S_{1}' \\ S_{1}' + D_{4,n}^{*} & \xrightarrow{k_{\text{slow}}} & D_{3,n}' + S_{1}' \\ \end{split}$$

Red phase signal transfer reactions:

$$\begin{array}{cccc} R+D_{1,p}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{1,p}+R \\ R+D_{1,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{1,n}+R \\ R+D_{1,p}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{1,p}^*+R \\ R+D_{1,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{1,p}^*+R \\ R+D_{2,p}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{2,p}+R \\ R+D_{2,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{2,p}+R \\ R+D_{2,p}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{2,p}^*+R \\ R+D_{2,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{2,p}^*+R \\ R+D_{2,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{2,p}^*+R \\ R+D_{2,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{2,p}^*+R \\ R+D_{3,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{3,p}^*+R \\ R+D_{4,p}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{4,p}^*+R \\ R+D_{4,n}' & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & D_{4,p}^*+R \\ \end{array}$$

Positive-negative cancellation reactions:

$$\begin{array}{ccccccccc} I_{1,p}+I_{1,n} & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ I_{1,p}^*+I_{1,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ I_{2,p}+I_{2,n} & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ I_{2,p}^*+I_{2,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ O_{1,p}^*+O_{1,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ O_{1,p}^*+O_{1,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ O_{2,p}^*+O_{2,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ O_{2,p}^*+O_{2,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ O_{2,p}^*+O_{2,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ M_{1,p}^*+M_{1,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ M_{1,p}^*+M_{1,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ M_{2,p}^*+M_{2,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ M_{2,p}^*+M_{2,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ D_{1,p}^*+D_{1,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ D_{1,p}^*+D_{1,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ D_{2,p}^*+D_{2,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ D_{2,p}^*+D_{2,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ D_{3,p}^*+D_{3,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ D_{4,p}^*+D_{4,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ D_{4,p}^*+D_{4,n}^* & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & \varnothing \\ \end{array}$$

Appendix B

List of Molecular-Level Reactions of Digital Logic Systems

B.1 Binary Counter

Clock reactions:

$$\begin{array}{cccc} 2S_r & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & 2S_r + r \\ r + R & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & R \\ v + R & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & G \\ 2S_g & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & 2S_g + g \\ g + G & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & G \\ r + G & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & B \\ 2S_b & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & 2S_b + b \\ b + B & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & B \\ g + B & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & V \\ 2S_v & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & 2S_v + v \\ v + V & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & V \\ b + V & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & R \end{array}$$

$$\begin{array}{cccc} 2R & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & I_R \\ 2I_R & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 4R \\ I_R + V & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 3R \\ 2G & \stackrel{\mathrm{k_{slow}}}{\longrightarrow} & I_G \\ 2I_G & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 4G \\ I_G + R & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 3G \\ 2B & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 3G \\ 2B & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 4B \\ 2I_B & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 4B \\ 2I_B + G & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 3B \\ 2V & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & I_V \\ 2I_V & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 4V \\ I_V + B & \stackrel{\mathrm{k_{fast}}}{\longrightarrow} & 3V. \end{array}$$

D flip-flop 1:

D flip-flop 2:

D flip-flop 3:

B.2 Linear Feedback Shift Register

Clock reactions:

D flip-flop 1:

D flip-flop 2:

$$\begin{array}{cccccccc} A_0+R & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & M_0'^B+A_0+R\\ A_1+R & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & M_1'^B+A_1+R\\ 2M_0'^B & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & \varnothing\\ 2M_1'^B & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & \varnothing\\ 2M_1'^B+M_0^B & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & M_1^B\\ M_0'^B+M_1^B & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & M_0^B\\ M_0^B+B & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & B_0'+M_0^B+B\\ M_1^B+B & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & B_1'+M_1^B+B\\ 2B_0' & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & \varnothing\\ 2B_1' & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & \varnothing\\ B_0'+B_1 & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & B_0\\ B_0+B_1 & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & 3B_0\\ S_B+B_0 & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\longrightarrow} & 3B_1. \end{array}$$

D flip-flop 3:

XOR gate:

$$\begin{array}{cccc} B_0+C_1 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & B_0+C_1+X_1'\\ B_1+C_0 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & B_1+C_0+X_1'\\ B_0+C_0 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & B_0+C_0+X_0'\\ B_1+C_1 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & B_1+C_1+X_0'\\ & X_0' & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & \varnothing\\ & X_1' & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & \varnothing\\ & X_0'+X_1 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & X_0\\ & X_1'+X_0 & \stackrel{\mathbf{k_{fast}}}{\longrightarrow} & X_1. \end{array}$$

B.3 Square Root Unit

ab11 + oa10	$\stackrel{k}{\longrightarrow}$	ab11 + oa11
aa10 + ab10	$\stackrel{k}{\longrightarrow}$	aa10 + ab10 + poa10
poa10 + poa10	$\stackrel{k}{\longrightarrow}$	nth
poa10 + oa11	$\stackrel{k}{\longrightarrow}$	oa10
oa11 + c300	$\stackrel{k}{\longrightarrow}$	oa11 + c301
ac11 + c300	$\stackrel{k}{\longrightarrow}$	ac11 + c301
oa10 + ac10	\xrightarrow{k}	oa10 + ac10 + pc300
pc300 + pc300	\xrightarrow{k}	nth
pc300 + c301	$\stackrel{k}{\longrightarrow}$	c300
c300 + c301	$\stackrel{k}{\longrightarrow}$	Sc30
c300 + Sc30	$\stackrel{k}{\longrightarrow}$	3c300
c301 + Sc30	$\stackrel{k}{\longrightarrow}$	3c301
dd10 + a60	\xrightarrow{k}	dd10 + a60 + pxa10
dd10 + a60 $dd11 + a60$	$\stackrel{k}{\longrightarrow}$	dd10 + a60 + pxa10 $dd11 + a60 + pxa11$
dd10 + a60 $dd11 + a60$ $dd11 + a61$	$\xrightarrow{k} \xrightarrow{k} \xrightarrow{k} \xrightarrow{k}$	dd10 + a60 + pxa10 dd11 + a60 + pxa11 dd11 + a61 + pxa10
dd10 + a60 dd11 + a60 dd11 + a61 dd10 + a61	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	$dd10 + a60 + pxa10 \\ dd11 + a60 + pxa11 \\ dd11 + a61 + pxa10 \\ dd10 + a61 + pxa11$
dd10 + a60 $dd11 + a60$ $dd11 + a61$ $dd10 + a61$ $pxa10 + pxa10$	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	$dd10 + a60 + pxa10 \\ dd11 + a60 + pxa11 \\ dd11 + a61 + pxa10 \\ dd10 + a61 + pxa11 \\ nth$
dd10 + a60 dd11 + a60 dd11 + a61 dd10 + a61 pxa10 + pxa10 pxa11 + pxa11	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	
dd10 + a60 dd11 + a60 dd11 + a61 dd10 + a61 pxa10 + pxa10 pxa11 + pxa11 pxa10 + xa11	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	dd10 + a60 + pxa10 dd11 + a60 + pxa11 dd11 + a61 + pxa10 dd10 + a61 + pxa11 nth nth xa10
dd10 + a60 dd11 + a60 dd11 + a61 dd10 + a61 pxa10 + pxa10 pxa11 + pxa11 pxa10 + xa11 pxa11 + xa10	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	dd10 + a60 + pxa10 dd11 + a60 + pxa11 dd11 + a61 + pxa10 dd10 + a61 + pxa11 nth nth xa10 xa11
dd10 + a60 dd11 + a60 dd11 + a61 dd10 + a61 pxa10 + pxa10 pxa11 + pxa11 pxa10 + xa11 pxa10 + xa11 pxa11 + xa10 xa10 + v10	$\begin{array}{c} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \end{array}$	dd10 + a60 + pxa10 dd11 + a60 + pxa11 dd11 + a61 + pxa10 dd10 + a61 + pxa11 nth nth xa10 xa10 xa11 xa10 + v10 + m200
dd10 + a60 dd11 + a60 dd11 + a61 dd10 + a61 pxa10 + pxa10 pxa11 + pxa11 pxa10 + xa11 pxa10 + xa11 pxa11 + xa10 xa10 + v10 xa11 + v10	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}$	dd10 + a60 + pxa10 dd11 + a60 + pxa11 dd11 + a61 + pxa10 dd10 + a61 + pxa11 nth nth xa10 xa10 xa11 xa10 + v10 + pr200 xa11 + v10 + pr201
$dd10 + a60 \\ dd11 + a60 \\ dd11 + a61 \\ dd10 + a61 \\ pxa10 + pxa10 \\ pxa10 + pxa11 \\ pxa10 + xa11 \\ pxa10 + xa11 \\ pxa11 + xa10 \\ xa10 + v10 \\ xa11 + v10 \\ xa11 + v11 \\ dxa11 + v11 \\ $	$\begin{array}{c} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \overset{k}{\longrightarrow} \overset{k}{\longrightarrow} \overset{k}{\longrightarrow} \overset{k}{\longrightarrow} \overset{k}{\longrightarrow} k$	dd10 + a60 + pxa10 dd11 + a60 + pxa11 dd11 + a61 + pxa10 dd10 + a61 + pxa11 nth nth xa10 xa10 xa11 xa10 + v10 + pr200 xa11 + v10 + pr201 xa11 + v11 + mr200
$dd10 + a60 \\ dd11 + a60 \\ dd11 + a61 \\ dd10 + a61 \\ pxa10 + pxa10 \\ pxa11 + pxa11 \\ pxa10 + xa11 \\ pxa11 + xa10 \\ xa10 + v10 \\ xa11 + v10 \\ xa11 + v11 \\ xa10 +$	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\$	dd10 + a60 + pxa10 dd11 + a60 + pxa11 dd11 + a61 + pxa10 dd10 + a61 + pxa11 nth nth xa10 xa10 xa11 xa10 + v10 + pr200 xa11 + v10 + pr201 xa10 + v11 + pr200

ac31 + c200	\xrightarrow{k}	ac31 + c201
oa30 + ac30	$\stackrel{k}{\longrightarrow}$	oa30 + ac30 + pc200
pc200 + pc200	$\stackrel{k}{\longrightarrow}$	nth
pc200 + c201	$\stackrel{k}{\longrightarrow}$	<i>c</i> 200
c200 + c201	$\stackrel{k}{\longrightarrow}$	Sc20
c200 + Sc20	$\stackrel{k}{\longrightarrow}$	3c200
c201 + Sc20	$\stackrel{k}{\longrightarrow}$	3 <i>c</i> 201
dd30 + a40	$\stackrel{k}{\longrightarrow}$	dd30 + a40 + pxa30
dd31 + a40	$\stackrel{k}{\longrightarrow}$	dd31 + a40 + pxa31
dd31 + a41	$\stackrel{k}{\longrightarrow}$	dd31 + a41 + pxa30
dd30 + a41	$\stackrel{k}{\longrightarrow}$	dd30 + a41 + pxa31
pxa30 + pxa30	$\stackrel{k}{\longrightarrow}$	nth
pxa31 + pxa31	$\stackrel{k}{\longrightarrow}$	nth
pxa30 + xa31	$\stackrel{k}{\longrightarrow}$	xa30
pxa31 + xa30	$\stackrel{k}{\longrightarrow}$	xa31
xa30 + q30	$\stackrel{k}{\longrightarrow}$	m = 20 + m = 100
xa31 + a30		xa50 + q50 + pr100
	$\stackrel{k}{\longrightarrow}$	xa30 + q30 + pr100 xa31 + q30 + pr101
xa31 + q31	$\stackrel{k}{\longrightarrow}$	xa30 + q30 + pr100 xa31 + q30 + pr101 xa31 + q31 + pr100
xa31 + q31 $xa30 + q31$	$\stackrel{k}{\longrightarrow} \xrightarrow{k}$	xa30 + q30 + pr100 $xa31 + q30 + pr101$ $xa31 + q31 + pr100$ $xa30 + q31 + pr101$
xa31 + q31 $xa30 + q31$ $pr100 + pr100$	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	$xa_{30} + q_{30} + pr_{100}$ $xa_{31} + q_{30} + pr_{101}$ $xa_{31} + q_{31} + pr_{100}$ $xa_{30} + q_{31} + pr_{101}$ nth
xa31 + q31 xa30 + q31 pr100 + pr100 pr101 + pr101	$\begin{array}{c} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \end{array}$	$xa_{30} + q_{30} + pr_{100}$ $xa_{31} + q_{30} + pr_{101}$ $xa_{31} + q_{31} + pr_{100}$ $xa_{30} + q_{31} + pr_{101}$ nth nth
xa31 + q31 xa30 + q31 pr100 + pr100 pr101 + pr101 pr100 + r101	$\begin{array}{c} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \end{array}$	$xa_{30} + q_{30} + pr_{100}$ $xa_{31} + q_{30} + pr_{101}$ $xa_{31} + q_{31} + pr_{100}$ $xa_{30} + q_{31} + pr_{101}$ nth nth r_{100}
xa31 + q31 $xa30 + q31$ $pr100 + pr100$ $pr101 + pr101$ $pr100 + r101$ $pr101 + r101$	$\begin{array}{c} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \end{array}$	$xa_{30} + q_{30} + pr_{100}$ $xa_{31} + q_{30} + pr_{101}$ $xa_{31} + q_{31} + pr_{100}$ $xa_{30} + q_{31} + pr_{101}$ nth nth r_{100} r_{101}

pac41 + ac40	$\stackrel{k}{\longrightarrow}$	ac41
aa41 + oa40	$\stackrel{k}{\longrightarrow}$	aa41 + oa41
ab41 + oa40	$\stackrel{k}{\longrightarrow}$	ab41 + oa41
aa40 + ab40	$\stackrel{k}{\longrightarrow}$	aa40 + ab40 + poa40
poa40 + poa40	$\stackrel{k}{\longrightarrow}$	nth
poa40 + oa41	$\stackrel{k}{\longrightarrow}$	oa40
oa41 + c210	$\stackrel{k}{\longrightarrow}$	oa41 + c211
ac41 + c210	$\stackrel{k}{\longrightarrow}$	ac41 + c211
oa40 + ac40	$\stackrel{k}{\longrightarrow}$	oa40 + ac40 + pc210
pc210 + pc210	$\stackrel{k}{\longrightarrow}$	nth
pc210 + c211	$\stackrel{k}{\longrightarrow}$	<i>c</i> 210
c210 + c211	$\stackrel{k}{\longrightarrow}$	Sc21
c210 + Sc21	$\stackrel{k}{\longrightarrow}$	3c210
c210 + Sc21 $c211 + Sc21$	$\stackrel{k}{\longrightarrow}$	3c210 3c211
c210 + Sc21 $c211 + Sc21$ $dd40 + a50$	$\xrightarrow{k} \xrightarrow{k} \xrightarrow{k}$	3c210 $3c211$ $dd40 + a50 + pxa40$
c210 + Sc21 $c211 + Sc21$ $dd40 + a50$ $dd41 + a50$	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	3c210 3c211 dd40 + a50 + pxa40 dd41 + a50 + pxa41
c210 + Sc21 c211 + Sc21 dd40 + a50 dd41 + a50 dd41 + a51	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	3c210 3c211 dd40 + a50 + pxa40 dd41 + a50 + pxa41 dd41 + a51 + pxa40
c210 + Sc21 c211 + Sc21 dd40 + a50 dd41 + a50 dd41 + a51 dd40 + a51	$\begin{array}{c} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \end{array}$	3c210 3c211 dd40 + a50 + pxa40 dd41 + a50 + pxa41 dd41 + a51 + pxa40 dd40 + a51 + pxa41
$c210 + Sc21 \\ c211 + Sc21 \\ dd40 + a50 \\ dd41 + a50 \\ dd41 + a51 \\ dd40 + a51 \\ pxa40 + pxa40$	$\begin{array}{c} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \end{array}$	3c210 3c211 dd40 + a50 + pxa40 dd41 + a50 + pxa41 dd41 + a51 + pxa40 dd40 + a51 + pxa41 nth
$c210 + Sc21 \\ c211 + Sc21 \\ dd40 + a50 \\ dd41 + a50 \\ dd41 + a51 \\ dd40 + a51 \\ pxa40 + pxa40 \\ pxa41 + pxa41$	$\begin{array}{c} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \end{array}$	3c210 3c211 dd40 + a50 + pxa40 dd41 + a50 + pxa41 dd41 + a51 + pxa40 dd40 + a51 + pxa41 nth nth
$c210 + Sc21 \\ c211 + Sc21 \\ dd40 + a50 \\ dd41 + a50 \\ dd41 + a51 \\ dd40 + a51 \\ pxa40 + pxa40 \\ pxa41 + pxa41 \\ pxa40 + xa41 \\ pxa40 + xa41$	$\begin{array}{c} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \end{array}$	3c210 3c211 dd40 + a50 + pxa40 dd41 + a50 + pxa41 dd41 + a51 + pxa40 dd40 + a51 + pxa41 nth nth nth xa40
$c210 + Sc21 \\ c211 + Sc21 \\ dd40 + a50 \\ dd41 + a50 \\ dd41 + a51 \\ dd40 + a51 \\ pxa40 + pxa40 \\ pxa41 + pxa41 \\ pxa40 + xa41 \\ pxa41 + xa40 \\ \end{cases}$	$\begin{array}{c} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \end{array}$	3c210 3c211 dd40 + a50 + pxa40 dd41 + a50 + pxa41 dd41 + a51 + pxa40 dd40 + a51 + pxa41 nth nth xa40 xa41
$c210 + Sc21 \\ c211 + Sc21 \\ dd40 + a50 \\ dd41 + a50 \\ dd41 + a51 \\ dd40 + a51 \\ pxa40 + pxa40 \\ pxa41 + pxa41 \\ pxa40 + xa41 \\ pxa41 + xa40 \\ xa40 + c200 \\ \end{cases}$	$\begin{array}{c} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \end{array}$	3c210 3c211 dd40 + a50 + pxa40 dd41 + a50 + pxa41 dd41 + a51 + pxa40 dd40 + a51 + pxa41 nth nth xa40 xa41 xa40 + c200 + pr110

c211 + dd51	$\stackrel{k}{\longrightarrow}$	c211 + dd51 + pab51
pab51 + pab51	$\stackrel{k}{\longrightarrow}$	nth
pab51 + ab50	$\stackrel{k}{\longrightarrow}$	ab51
c210 + ac51	$\stackrel{k}{\longrightarrow}$	c210 + ac50
r200 + ac51	$\stackrel{k}{\longrightarrow}$	c210 + ac50
c211 + r201	$\stackrel{k}{\longrightarrow}$	c211 + r201 + pac51
pac51 + pac51	$\stackrel{k}{\longrightarrow}$	nth
pac51 + ac50	$\stackrel{k}{\longrightarrow}$	ac51
aa51 + oa50	$\stackrel{k}{\longrightarrow}$	aa51 + oa51
ab51 + oa50	$\stackrel{k}{\longrightarrow}$	ab51 + oa51
aa50 + ab50	$\stackrel{k}{\longrightarrow}$	aa50 + ab50 + poa50
poa50 + poa50	$\stackrel{k}{\longrightarrow}$	nth
poa50 + oa51	$\stackrel{k}{\longrightarrow}$	oa50
oa51 + q20	$\stackrel{k}{\longrightarrow}$	oa51 + q21
ac51 + q20	$\stackrel{k}{\longrightarrow}$	ac51 + q21
oa50 + ac50	$\stackrel{k}{\longrightarrow}$	oa50 + ac50 + pq20
pq20 + pq20	$\stackrel{k}{\longrightarrow}$	nth
pq20 + q21	$\stackrel{k}{\longrightarrow}$	q20
q20 + q21	$\overset{k}{\longrightarrow}$	Sq2
q20 + Sq2	$\stackrel{k}{\longrightarrow}$	3q20
q21 + Sq2	$\stackrel{k}{\longrightarrow}$	3q21
q20 + v10	$\stackrel{k}{\longrightarrow}$	q20 + v10 + pdd60
q21 + v10	$\stackrel{k}{\longrightarrow}$	q21 + v10 + pdd61
q21 + v11	$\stackrel{k}{\longrightarrow}$	q21 + v11 + pdd60

poa60 + oa61	$\stackrel{k}{\longrightarrow}$	<i>oa</i> 60
oa61 + c100	$\stackrel{k}{\longrightarrow}$	oa61 + c101
ac61 + c100	$\stackrel{k}{\longrightarrow}$	ac61 + c101
oa60 + ac60	$\stackrel{k}{\longrightarrow}$	oa60 + ac60 + pc100
pc100 + pc100	$\stackrel{k}{\longrightarrow}$	nth
pc100 + c101	$\stackrel{k}{\longrightarrow}$	<i>c</i> 100
c100 + c101	$\stackrel{k}{\longrightarrow}$	Sc10
c100 + Sc10	\xrightarrow{k}	3c100
c101 + Sc10	$\stackrel{k}{\longrightarrow}$	3c101
dd60 + a20	$\stackrel{k}{\longrightarrow}$	dd60 + a20 + pxa60
dd61 + a20	$\stackrel{k}{\longrightarrow}$	dd61 + a20 + pxa61
dd61 + a21	$\stackrel{k}{\longrightarrow}$	dd61 + a21 + pxa60
dd60 + a21	\xrightarrow{k}	dd60 + a21 + pxa61
pxa60 + pxa60	$\stackrel{k}{\longrightarrow}$	nth
pxa61 + pxa61	$\stackrel{\mathrm{k}}{\longrightarrow}$	nth
pxa60 + xa61	$\stackrel{k}{\longrightarrow}$	xa60
pxa61 + xa60	$\stackrel{k}{\longrightarrow}$	xa61
xa60 + q20	$\stackrel{k}{\longrightarrow}$	xa60 + q20 + pr000
		^ ^
xa61 + a20	\xrightarrow{k}	xa61 + a20 + pr001
xa61 + q20 $xa61 + q21$	$\xrightarrow{k}{\overset{k}{\longrightarrow}}$	xa61 + q20 + pr001 xa61 + q21 + pr000
xa61 + q20 $xa61 + q21$ $xa60 + q21$	$\xrightarrow{k} \\ \xrightarrow{k} \\ $	xa61 + q20 + pr001 xa61 + q21 + pr000 xa60 + q21 + pr001
xa61 + q20 $xa61 + q21$ $xa60 + q21$ $mr000 + mr000$	$ \begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array} $	xa61 + q20 + pr001 xa61 + q21 + pr000 xa60 + q21 + pr001 nth
xa61 + q20 $xa61 + q21$ $xa60 + q21$ $pr000 + pr000$ $pr001 + pr001$	$ \begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array} $	xa61 + q20 + pr001 xa61 + q21 + pr000 xa60 + q21 + pr001 nth nth
xa61 + q20 xa61 + q21 xa60 + q21 pr000 + pr000 pr001 + pr001 pr000 + r001	$\begin{array}{c} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \end{array}$	xa61 + q20 + pr001 xa61 + q21 + pr000 xa60 + q21 + pr001 nth nth r000
$$\begin{array}{rcrcrc} xa70 + c100 & \stackrel{\mathrm{k}}{\longrightarrow} & xa70 + c100 + pr010 \\ xa71 + c100 & \stackrel{\mathrm{k}}{\longrightarrow} & xa71 + c100 + pr011 \\ xa71 + c101 & \stackrel{\mathrm{k}}{\longrightarrow} & xa71 + c101 + pr010 \\ xa70 + c101 & \stackrel{\mathrm{k}}{\longrightarrow} & xa70 + c101 + pr011 \\ pr010 + pr010 & \stackrel{\mathrm{k}}{\longrightarrow} & nth \\ pr011 + pr011 & \stackrel{\mathrm{k}}{\longrightarrow} & r010 \\ pr011 + r010 & \stackrel{\mathrm{k}}{\longrightarrow} & r011 \\ r010 + r011 & \stackrel{\mathrm{k}}{\longrightarrow} & sr01 \\ r010 + r011 & \stackrel{\mathrm{k}}{\longrightarrow} & 3r010 \\ r011 + Sr01 & \stackrel{\mathrm{k}}{\longrightarrow} & 3r011 \\ q20 + q20 & \stackrel{\mathrm{k}}{\longrightarrow} & q20 + q20 + pdd80 \\ q21 + q20 & \stackrel{\mathrm{k}}{\longrightarrow} & q21 + q20 + pdd81 \\ q20 + q21 & \stackrel{\mathrm{k}}{\longrightarrow} & q21 + q21 + pdd81 \\ q20 + q21 & \stackrel{\mathrm{k}}{\longrightarrow} & q20 + q21 + pdd81 \\ pdd80 + pdd80 & \stackrel{\mathrm{k}}{\longrightarrow} & nth \\ pdd81 + pdd81 & \stackrel{\mathrm{k}}{\longrightarrow} & nth \\ pdd81 + dd80 & \stackrel{\mathrm{k}}{\longrightarrow} & dd81 \\ pdd80 + aa81 & \stackrel{\mathrm{k}}{\longrightarrow} & d10 + aa80 \\ da80 + aa81 & \stackrel{\mathrm{k}}{\longrightarrow} & r101 + dd81 + paa81 \\ paa81 + paa81 & \stackrel{\mathrm{k}}{\longrightarrow} & aa81 \\ \end{array}$$

c110 + ab81	$\stackrel{k}{\longrightarrow}$	c110 + ab80
dd80 + ab81	$\stackrel{k}{\longrightarrow}$	dd80 + ab80
c111 + dd81	$\stackrel{k}{\longrightarrow}$	c111 + dd81 + pab81
pab81 + pab81	$\stackrel{k}{\longrightarrow}$	nth
pab81 + ab80	$\stackrel{k}{\longrightarrow}$	ab81
c110 + ac81	$\stackrel{k}{\longrightarrow}$	c110 + ac80
r100 + ac81	$\stackrel{k}{\longrightarrow}$	c110 + ac80
c111 + r101	$\stackrel{k}{\longrightarrow}$	c111 + r101 + pac81
pac81 + pac81	$\stackrel{k}{\longrightarrow}$	nth
pac81 + ac80	$\stackrel{k}{\longrightarrow}$	ac81
aa81 + oa80	$\stackrel{k}{\longrightarrow}$	aa81 + oa81
ab81 + oa80	$\stackrel{k}{\longrightarrow}$	ab81 + oa81
aa80 + ab80	$\stackrel{k}{\longrightarrow}$	aa80 + ab80 + poa80
poa80 + poa80	$\stackrel{k}{\longrightarrow}$	nth
poa80 + oa81	$\stackrel{k}{\longrightarrow}$	<i>oa</i> 80
oa81 + c120	$\stackrel{k}{\longrightarrow}$	oa81 + c121
ac81 + c120	$\stackrel{k}{\longrightarrow}$	ac81 + c121
oa80 + ac80	$\stackrel{k}{\longrightarrow}$	oa80 + ac80 + pc120
pc120 + pc120	$\stackrel{k}{\longrightarrow}$	nth
pc120 + c121	$\stackrel{k}{\longrightarrow}$	<i>c</i> 120
c120 + c121	$\overset{k}{\longrightarrow}$	Sc12
c120 + Sc12	$\stackrel{k}{\longrightarrow}$	3c120
c121 + Sc12	$\stackrel{k}{\longrightarrow}$	3c121
dd80 + r100	\xrightarrow{k}	dd80 + r100 + pxa80

pdd91 + dd90	$\stackrel{k}{\longrightarrow}$	dd91
pdd90 + dd91	$\stackrel{k}{\longrightarrow}$	dd90
r110 + aa91	$\stackrel{k}{\longrightarrow}$	r110 + aa90
dd90 + aa91	$\stackrel{k}{\longrightarrow}$	dd90 + aa90
r111 + dd91	$\stackrel{k}{\longrightarrow}$	r111 + dd91 + paa91
paa91 + paa91	$\stackrel{k}{\longrightarrow}$	nth
paa91 + aa90	$\stackrel{k}{\longrightarrow}$	<i>aa</i> 91
c120 + ab91	$\stackrel{k}{\longrightarrow}$	c120 + ab90
dd90 + ab91	$\stackrel{k}{\longrightarrow}$	dd90 + ab90
c121 + dd91	$\stackrel{k}{\longrightarrow}$	c121 + dd91 + pab91
pab91 + pab91	$\stackrel{k}{\longrightarrow}$	nth
pab91 + ab90	$\stackrel{k}{\longrightarrow}$	ab91
c120 + ac91	$\overset{k}{\longrightarrow}$	c120 + ac90
r110 + ac91	$\stackrel{k}{\longrightarrow}$	c120 + ac90
$a191 \pm m111$	k	c191 + r111 + nac01
$c_{121} + r_{111}$	\rightarrow	$c_{121} \pm r_{111} \pm pac_{91}$
pac91 + pac91	\xrightarrow{k}	c121 + 7111 + pac91 nth
pac91 + pac91 $pac91 + ac90$	$\xrightarrow{k} \xrightarrow{k}$	c121 + 7111 + pacs1 nth ac91
pac91 + pac91 $pac91 + ac90$ $aa91 + oa90$	$ \xrightarrow{k} \\ \xrightarrow{k} \\$	c121 + 7111 + pacs1 nth ac91 aa91 + oa91
pac91 + pac91 $pac91 + ac90$ $aa91 + oa90$ $ab91 + oa90$	$ \begin{array}{c} \xrightarrow{k} \\ \xrightarrow{k} \\ \xrightarrow{k} \\ \xrightarrow{k} \\ \xrightarrow{k} \end{array} $	c121 + 7111 + pacs1 nth ac91 aa91 + oa91 ab91 + oa91
c121 + r111 pac91 + pac91 pac91 + ac90 aa91 + oa90 ab91 + oa90 aa90 + ab90	$\begin{array}{c} \xrightarrow{k} \\ \xrightarrow{k} \\ \xrightarrow{k} \\ \xrightarrow{k} \\ \xrightarrow{k} \\ \xrightarrow{k} \end{array}$	c121 + 7111 + pacs1 nth ac91 aa91 + oa91 ab91 + oa91 aa90 + ab90 + poa90
c121 + r111 pac91 + pac91 pac91 + ac90 aa91 + oa90 ab91 + oa90 aa90 + ab90 poa90 + poa90	$\begin{array}{c} \xrightarrow{k} \\ \xrightarrow{k} \\ \xrightarrow{k} \\ \xrightarrow{k} \\ \xrightarrow{k} \\ \xrightarrow{k} \\ \xrightarrow{k} \end{array}$	nth $ac91$ $ab91 + oa91$ $aa90 + ab90 + poa90$ nth
c121 + r111 pac91 + pac91 pac91 + ac90 aa91 + oa90 ab91 + oa90 aa90 + ab90 poa90 + poa90 poa90 + oa91	$\begin{array}{c} \xrightarrow{k} \\ \xrightarrow{k} \end{array}$	c121 + 7111 + pacs1 nth ac91 aa91 + oa91 aa90 + ab90 + poa90 nth oa90
c121 + r111 pac91 + pac91 pac91 + ac90 aa91 + oa90 ab91 + oa90 aa90 + ab90 poa90 + poa90 poa90 + oa91 oa91 + q10	$ \begin{array}{c} \xrightarrow{k} \\ \xrightarrow$	c121 + 7111 + pacs1 nth ac91 aa91 + oa91 aa90 + ab90 + poa90 nth oa90 oa91 + q11

pdd131 + dd130	$\stackrel{k}{\longrightarrow}$	dd131
pdd130 + dd131	$\stackrel{k}{\longrightarrow}$	dd130
r010 + aa131	$\stackrel{k}{\longrightarrow}$	r010 + aa130
dd130 + aa131	$\stackrel{k}{\longrightarrow}$	dd130 + aa130
r011 + dd131	$\stackrel{k}{\longrightarrow}$	r011 + dd131 + paa131
paa131 + paa131	$\stackrel{k}{\longrightarrow}$	nth
paa131 + aa130	$\stackrel{k}{\longrightarrow}$	aa131
c020 + ab131	$\stackrel{k}{\longrightarrow}$	c020 + ab130
dd130 + ab131	$\stackrel{k}{\longrightarrow}$	dd130 + ab130
c021 + dd131	$\stackrel{k}{\longrightarrow}$	c021 + dd131 + pab131
pab131 + pab131	$\stackrel{k}{\longrightarrow}$	nth
pab131 + ab130	$\stackrel{k}{\longrightarrow}$	ab131
c020 + ac131	$\stackrel{k}{\longrightarrow}$	c020 + ac130
c020 + ac131 $r010 + ac131$	$\stackrel{k}{\longrightarrow}$	c020 + ac130 c020 + ac130
c020 + ac131 r010 + ac131 c021 + r011	$\xrightarrow{k} \\ \xrightarrow{k} \\ $	c020 + ac130 c020 + ac130 c021 + r011 + pac131
c020 + ac131 r010 + ac131 c021 + r011 pac131 + pac131	$\begin{array}{c} \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \\ \overset{k}{\longrightarrow} \end{array}$	c020 + ac130 c020 + ac130 c021 + r011 + pac131 nth
c020 + ac131 r010 + ac131 c021 + r011 pac131 + pac131 pac131 + ac130	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	c020 + ac130 c020 + ac130 c021 + r011 + pac131 nth ac131
c020 + ac131 r010 + ac131 c021 + r011 pac131 + pac131 pac131 + ac130 aa131 + oa130	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	c020 + ac130 c020 + ac130 c021 + r011 + pac131 nth ac131 aa131 + oa131
c020 + ac131 r010 + ac131 c021 + r011 pac131 + pac131 pac131 + ac130 aa131 + oa130 ab131 + oa130	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	c020 + ac130 c020 + ac130 c021 + r011 + pac131 nth ac131 aa131 + oa131 ab131 + oa131
c020 + ac131 r010 + ac131 c021 + r011 pac131 + pac131 pac131 + ac130 aa131 + oa130 ab131 + oa130 aa130 + ab130	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	c020 + ac130 c020 + ac130 c021 + r011 + pac131 nth ac131 aa131 + oa131 ab131 + oa131 aa130 + ab130 + poa130
c020 + ac131 r010 + ac131 c021 + r011 pac131 + pac131 pac131 + ac130 aa131 + oa130 ab131 + oa130 aa130 + ab130 poa130 + poa130	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	c020 + ac130 c020 + ac130 c021 + r011 + pac131 nth ac131 aa131 + oa131 ab131 + oa131 aa130 + ab130 + poa130 nth
c020 + ac131 r010 + ac131 c021 + r011 pac131 + pac131 pac131 + ac130 aa131 + oa130 ab131 + oa130 aa130 + ab130 poa130 + poa130 poa130 + oa131	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \end{array}$	c020 + ac130 c020 + ac130 c021 + r011 + pac131 nth ac131 aa131 + oa131 ab131 + oa131 aa130 + ab130 + poa130 nth oa130
c020 + ac131 r010 + ac131 c021 + r011 pac131 + pac131 pac131 + ac130 aa131 + aa130 ab131 + aa130 aa130 + ab130 poa130 + paa130 poa130 + aa131 aa131 + c030	$\begin{array}{c} \stackrel{k}{\longrightarrow} \\ \begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \stackrel{k}{\longrightarrow} \\ \begin{array}{c} \stackrel{k}{\longrightarrow} \\ \stackrel{k}$	c020 + ac130 c020 + ac130 c021 + r011 + pac131 nth ac131 aa131 + oa131 ab131 + oa131 aa130 + ab130 + poa130 nth oa130 oa131 + c031

Appendix C

List of DNA-Level Reactions

In this chapter, we list DNA-level reactions for the moving-average filter and biquad filter with RGB scheme. Each molecular reaction discussed in Chapter 3 is mapped to DNA level using the method described in [4].

C.1 Moving-Average Filter

$$\begin{array}{cccc} r+L_1 & \overleftarrow{\underset{q_{\max}}{\overset{k_{\text{fast}}}{\longleftarrow}}} & H_1+B_1 \\ \hline Y+B_1 & \xrightarrow{q_{\max}} & O_1 \\ O_1+T_1 & \xrightarrow{q_{\max}} & Y \\ r+L_2 & \overleftarrow{\underset{q_{\max}}{\overset{k_{\text{fast}}}{\longleftarrow}}} & H_2+B_2 \\ R+B_2 & \xrightarrow{q_{\max}} & O_2 \\ O_2+T_2 & \xrightarrow{q_{\max}} & O_2 \\ O_2+T_2 & \xrightarrow{q_{\max}} & R \\ g+L_3 & \overleftarrow{\underset{q_{\max}}{\overset{k_{\text{fast}}}{\longleftarrow}}} & H_3+B_3 \\ G+B_3 & \xrightarrow{q_{\max}} & O_3 \\ O_3+T_3 & \xrightarrow{q_{\max}} & G \end{array}$$

$$IB + L_{12} \quad \stackrel{\text{kfast}}{\underset{\text{qmax}}{\text{qmax}}} \quad H_{12} + B_{12}$$

$$IB + B_{12} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad O_{12}$$

$$O_{12} + T_{12} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad B$$

$$IB + L_{13} \quad \stackrel{\text{kfast}}{\underset{\text{qmax}}{\text{qmax}}} \quad H_{13} + B_{13}$$

$$G + B_{13} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad B$$

$$X + L_{14} \quad \stackrel{\text{kslow}}{\underset{\text{qmax}}{\text{qmax}}} \quad H_{14} + B_{14}$$

$$X + B_{14} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad O_{14}$$

$$O_{14} + T_{14} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad O_{15}$$

$$O_{15} + T_{15} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad O_{15}$$

$$O_{15} + T_{15} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad O_{16}$$

$$O_{16} + T_{16} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad O_{16}$$

$$O_{16} + T_{16} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad O_{17}$$

$$O_{17} + T_{17} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad O_{17}$$

$$O_{17} + T_{17} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad O_{18}$$

$$O_{18} + T_{18} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad IY$$

$$IY + L_{19} \quad \stackrel{\text{kfast}}{\xrightarrow{\text{qmax}}} \quad H_{19} + B_{19}$$

$$IY + B_{19} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad O_{19}$$

$$O_{19} + T_{19} \quad \stackrel{\text{qmax}}{\xrightarrow{\text{qmax}}} \quad Y$$

$$IR + L_{28} \quad \stackrel{\underline{\mathbf{k}_{\text{fast}}}}{\underset{\mathbf{q}_{\text{max}}}{\overset{\mathbf{m}_{28}}{\longrightarrow}}} \quad H_{28} + B_{28}$$
$$X + B_{28} \quad \stackrel{\underline{\mathbf{q}_{\text{max}}}}{\overset{\mathbf{m}_{28}}{\longrightarrow}} \quad O_{28}$$
$$O_{28} + T_{28} \quad \stackrel{\underline{\mathbf{q}_{\text{max}}}}{\overset{\mathbf{m}_{28}}{\longrightarrow}} \quad A + C + R$$

C.2 Biquad Filter

$$I_B 1 + L_{23} \quad \begin{cases} k_{\text{fast}} \\ \overline{q_{\text{max}}} \\ Q_2 + B_{23} \\ Q_{23} + T_{23} \\ Q_{24} + T_{24} \\ Q_{24} + T_{25} \\ Q_{24} + T_{25} \\ Q_{25} + T_{25} \\ Q_{25} + T_{25} \\ Q_{25} + T_{25} \\ Q_{25} + T_{25} \\ Q_{26} + T_{26} \\ Q_{27} \\ Q_{27} + T_{27} \\ Q_{28} + T_{28} \\ Q_{28} \\ Q_{28} + T_{28} \\ Q_{28} \\ Q_{28} + T_{28} \\ Q_{28} \\ Q_{29} \\ Q_{29} + T_{29} \\ Q_{29} \\ Q_{29} \\ Q_{29} + T_{29} \\ Q_{29} \\ Q_{29} \\ Q_{29} + T_{29} \\ Q_{29} \\ Q_{30} \\$$

$$I_Y + L_{36} \xrightarrow[q_{max}]{\text{max}} H_{36} + B_{36}$$

$$B_1 + B_{36} \xrightarrow[q_{max}]{\text{max}} O_{36}$$

$$O_{36} + T_{36} \xrightarrow[q_{max}]{\text{max}} R_2 + F + C + Y$$

$$I_Y + L_{27} \xrightarrow[k_{\text{fast}}]{\text{max}} H_{27} + B_{27}$$

$$I_Y + L_{37} \qquad \overleftarrow{\underset{q_{max}}{\longleftarrow}} \qquad H_{37} + B_{37}$$
$$B_2 + B_{37} \qquad \overleftarrow{\underset{q_{max}}{\bigoplus}} \qquad O_{37}$$
$$O_{37} + T_{37} \qquad \overleftarrow{\underset{q_{max}}{\bigoplus}} \qquad H + E + Y$$
$$I_Y + L_{38} \qquad \overleftarrow{\underset{q_{max}}{\longleftarrow}} \qquad H_{38} + B_{38}$$
$$X + B_{38} \qquad \overleftarrow{\underset{q_{max}}{\bigoplus}} \qquad O_{38}$$
$$O_{38} + T_{38} \qquad \overleftarrow{\underset{q_{max}}{\bigoplus}} \qquad R_1 + A + Y$$

 $O_{46} + T_{46} \xrightarrow{q_{\max}} I_R 2$

$$\begin{array}{ccccccccc} C_2 + L_{55} & \stackrel{\mathrm{k_{fast}}}{\mathrm{qmax}} & H_{55} + B_{55} \\ \hline C_2 + B_{55} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & O_{55} \\ \hline O_{55} + T_{55} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & C_4 \\ \hline C_4 + L_{56} & \stackrel{\mathrm{k_{fast}}}{\mathrm{qmax}} & H_{56} + B_{56} \\ \hline C_4 + B_{56} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & O_{56} \\ \hline O_{56} + T_{56} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & Y \\ \hline E + L_{57} & \stackrel{\mathrm{k_{fast}}}{\mathrm{qmax}} & H_{57} + B_{57} \\ \hline E + B_{57} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & C_2 \\ \hline E_2 + L_{58} & \stackrel{\mathrm{k_{fast}}}{\mathrm{qmax}} & H_{58} + B_{58} \\ \hline C_{2} + B_{58} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & O_{58} \\ \hline O_{58} + T_{58} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & O_{58} \\ \hline O_{58} + T_{58} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & C_{59} \\ \hline O_{59} + T_{59} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & D_{59} \\ \hline O_{59} + T_{59} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & Y \\ \hline F + L_{60} & \stackrel{\mathrm{k_{fast}}}{\mathrm{qmax}} & H_{60} + B_{60} \\ \hline F + B_{60} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & O_{61} \\ \hline O_{60} + T_{60} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & F_4 \\ \hline F_2 + B_{61} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & C_{61} \\ \hline O_{61} + T_{61} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & F_4 \\ \hline F_4 + L_{62} & \stackrel{\mathrm{k_{fast}}}{\mathrm{qmax}} & H_{62} + B_{62} \\ \hline F_4 + B_{62} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & O_{62} \\ \hline O_{62} + T_{62} & \stackrel{\mathrm{qmax}}{\mathrm{qmax}} & X \end{array}$$

$$\begin{array}{cccc} H+L_{63} & \stackrel{\mathbf{k}_{\mathrm{fast}}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & H_{63}+B_{63} \\ H+B_{63} & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_{63} \\ O_{63}+T_{63} & \stackrel{\mathrm{qmax}}{\longrightarrow} & H_2 \\ H_2+L_{64} & \stackrel{\mathrm{k}_{\mathrm{fast}}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & H_{64}+B_{64} \\ H_2+B_{64} & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_{64} \\ O_{64}+T_{64} & \stackrel{\mathrm{qmax}}{\longrightarrow} & H_4 \\ H_4+L_{65} & \stackrel{\mathrm{k}_{\mathrm{fast}}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & H_{65}+B_{65} \\ H_4+B_{65} & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_{65} \\ O_{65}+T_{65} & \stackrel{\mathrm{qmax}}{\longrightarrow} & X \end{array}$$

C.3 FFT Unit

C.3.1 Direct Implementation

$$\begin{aligned} src + L_1 & \overleftarrow{\underset{q_{max}}{\overset{ks}{\longleftarrow}}} & H_1 + B_1 \\ src + H_1 & \xrightarrow{q_{max}} & O_1 \\ O_1 + T_1 & \xrightarrow{q_{max}} & 2src + r \\ r + L_2 & \overleftarrow{\underset{q_{max}}{\overset{kf}{\longleftarrow}}} & H_2 + B_2 \\ R + H_2 & \xrightarrow{q_{max}} & O_2 \\ O_2 + T_2 & \xrightarrow{q_{max}} & R \\ v + L_3 & \overleftarrow{\underset{q_{max}}{\overset{ks}{\longleftarrow}}} & H_3 + B_3 \\ R + H_3 & \xrightarrow{q_{max}} & O_3 \\ O_3 + T_3 & \xrightarrow{q_{max}} & G \end{aligned}$$

$$\begin{array}{cccccccc} b+L_{12} & \stackrel{\mathrm{ks}}{\underset{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\mathrm{qmax}}}} & H_{12}+B_{12} \\ V+H_{12} & \stackrel{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{12} \\ O_{12}+T_{12} & \stackrel{\mathrm{qmax}}{\overset{\mathrm{max}}{\mathrm{qmax}}} & R \\ R+L_{13} & \stackrel{\mathrm{ks}}{\underset{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\mathrm{qmax}}}} & H_{13}+B_{13} \\ R+H_{13} & \stackrel{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{13} \\ O_{13}+T_{13} & \stackrel{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\mathrm{qmax}}} & IR \\ G+L_{14} & \stackrel{\mathrm{ks}}{\underset{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\mathrm{qmax}}}} & H_{14}+B_{14} \\ G+H_{14} & \stackrel{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{14} \\ O_{14}+T_{14} & \stackrel{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{14} \\ O_{14}+T_{14} & \stackrel{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{15} \\ B+H_{15} & \stackrel{\mathrm{ks}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & H_{15}+B_{15} \\ B+H_{15} & \stackrel{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\mathrm{qmax}}} & IB \\ V+L_{16} & \stackrel{\mathrm{ks}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & H_{16}+B_{16} \\ V+H_{16} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{16} \\ O_{16}+T_{16} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{16} \\ O_{16}+T_{16} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{17} \\ IR+H_{17} & \stackrel{\mathrm{kf}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & H_{17}+B_{17} \\ IR+H_{17} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{17} \\ O_{17}+T_{17} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{18} \\ IG+L_{18} & \stackrel{\mathrm{kf}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{18} \\ O_{18}+T_{18} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{19} \\ IB+H_{19} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{19} \\ O_{19}+T_{19} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & AB \end{array}$$
$$\begin{array}{cccccccc} O2c + L_{92} & \stackrel{\mathrm{kf}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & H_{92} + B_{92} \\ O2nc + H_{92} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{92} \\ O_{92} + T_{92} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & H_{93} + B_{93} \\ O3n + L_{93} & \stackrel{\mathrm{kf}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{93} \\ O_{93} + T_{93} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{93} \\ O_{93} + T_{93} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & H_{94} + B_{94} \\ O3c + L_{94} & \stackrel{\mathrm{kf}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & H_{94} + B_{94} \\ O3c + L_{94} & \stackrel{\mathrm{kf}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & H_{94} + B_{94} \\ O3nc + H_{94} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & O_{94} \\ O_{94} + T_{94} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & O_{94} \\ O_{94} + T_{94} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & O_{95} \\ O_{95} + T_{95} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & O_{95} \\ O_{95} + T_{95} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & O_{96} \\ O_{96} + T_{96} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & O_{96} \\ O_{96} + T_{96} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & O_{97} \\ M1n + H_{97} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & O_{97} \\ O_{97} + T_{97} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & H_{98} + B_{98} \\ M1nc + L_{98} & \stackrel{\mathrm{kf}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & H_{98} + B_{98} \\ M1nc + H_{98} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & O_{98} \\ O_{98} + T_{98} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & nth \\ M2 + L_{99} & \stackrel{\mathrm{kf}}{\underset{\mathrm{qmax}}{\mathrm{qmax}}} & H_{99} + B_{99} \\ M_{2n} + H_{99} & \stackrel{\mathrm{qmax}}{\underset{\mathrm{qmax}}{\mathrm{max}}} & nth \\ \end{array}$$

C.3.2 Two-Parallel Implementation

$$\begin{array}{ccccccc} b+L_8 & \stackrel{\mathrm{kf}}{\overbrace{\mathrm{qmax}}} & H_8+B_8 \\ B+H_8 & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_8 \\ O_8+T_8 & \stackrel{\mathrm{qmax}}{\longrightarrow} & B \\ g+L_9 & \stackrel{\mathrm{ks}}{\overbrace{\mathrm{qmax}}} & H_9+B_9 \\ B+H_9 & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_9 \\ O_9+T_9 & \stackrel{\mathrm{qmax}}{\longrightarrow} & V \\ src+L_{10} & \stackrel{\mathrm{ks}}{\overbrace{\mathrm{qmax}}} & H_{10}+B_{10} \\ src+H_{10} & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_{10} \\ O_{10}+T_{10} & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_{10} \\ O_{10}+T_{10} & \stackrel{\mathrm{qmax}}{\longleftarrow} & O_{11} \\ V+H_{11} & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_{11} \\ V+H_{11} & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_{11} \\ O_{11}+T_{11} & \stackrel{\mathrm{qmax}}{\longrightarrow} & V \\ b+L_{12} & \stackrel{\mathrm{ks}}{\overbrace{\mathrm{qmax}}} & H_{12}+B_{12} \\ V+H_{12} & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_{12} \\ O_{12}+T_{12} & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_{12} \\ O_{12}+T_{12} & \stackrel{\mathrm{qmax}}{\longrightarrow} & H_{13}+B_{13} \\ R+H_{13} & \stackrel{\mathrm{ks}}{\longleftarrow} & H_{13}+B_{13} \\ R+H_{13} & \stackrel{\mathrm{ks}}{\longleftarrow} & H_{13}+B_{13} \\ G+L_{14} & \stackrel{\mathrm{ks}}{\Huge{\mathrm{qmax}}} & H_{14}+B_{14} \\ G+H_{14} & \stackrel{\mathrm{ks}}{\Huge{\mathrm{qmax}}} & H_{14}+B_{14} \\ G+H_{14} & \stackrel{\mathrm{ks}}{\Huge{\mathrm{qmax}}} & H_{15}+B_{15} \\ B+H_{15} & \stackrel{\mathrm{ks}}{\Huge{\mathrm{qmax}}} & H_{15}+B_{15} \\ B+H_{15} & \stackrel{\mathrm{ks}}{\Huge{\mathrm{qmax}}} & IB \end{array}$$

$$\begin{array}{cccccccc} V+L_{16} & \stackrel{\mathrm{ks}}{\underset{\mathrm{qmax}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}{\overset{\mathrm{qmax}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}{\overset{\mathrm{qmax}}}}{\overset{\mathrm{qmax}}}}{\overset{\mathrm{qma$$

$$I1c + H_{39} \xrightarrow{q_{\max}} O_{39}$$
$$O_{39} + T_{39} \xrightarrow{q_{\max}} D1pc + sD1p$$

$$\begin{split} sD1p + L_{40} & \stackrel{\text{ks}}{\underset{\text{qmax}}{\text{qmax}}} & H_{40} + B_{40} \\ I1nc + H_{40} & \stackrel{\text{qmax}}{\longrightarrow} & O_{40} \\ O_{40} + T_{40} & \stackrel{\text{qmax}}{\longrightarrow} & D1pnc + sD1p \\ sD2p + L_{41} & \stackrel{\text{ks}}{\underset{\text{qmax}}{\text{qmax}}} & H_{41} + B_{41} \\ I1 + H_{41} & \stackrel{\text{qmax}}{\longrightarrow} & O_{41} \\ O_{41} + T_{41} & \stackrel{\text{qmax}}{\longrightarrow} & M1 + M2n + sD2p \\ sD2p + L_{42} & \stackrel{\text{ks}}{\underset{\text{qmax}}{\text{qmax}}} & H_{42} + B_{42} \\ I1n + H_{42} & \stackrel{\text{qmax}}{\longrightarrow} & O_{42} \\ O_{42} + T_{42} & \stackrel{\text{qmax}}{\longrightarrow} & M1n + M2 + sD2p \\ sD2p + L_{43} & \stackrel{\text{ks}}{\underset{\text{qmax}}{\text{qmax}}} & H_{43} + B_{43} \\ I1c + H_{43} & \stackrel{\text{qmax}}{\longrightarrow} & O_{43} \\ O_{43} + T_{43} & \stackrel{\text{qmax}}{\longrightarrow} & M1c + M2nc + sD2p \\ sD2p + L_{44} & \stackrel{\text{ks}}{\underset{\text{qmax}}{\text{qmax}}} & H_{44} + B_{44} \\ I1nc + H_{44} & \stackrel{\text{qmax}}{\longrightarrow} & O_{44} \\ O_{44} + T_{44} & \stackrel{\text{qmax}}{\longrightarrow} & O_{44} \\ O_{44} + T_{45} & \stackrel{\text{qmax}}{\longrightarrow} & M1nc + M2c + sD2p \\ B + L_{45} & \stackrel{\text{ks}}{\underset{\text{qmax}}{\text{qmax}}} & H_{45} + B_{45} \\ I2 + H_{45} & \stackrel{\text{qmax}}{\longrightarrow} & O_{45} \\ O_{45} + T_{45} & \stackrel{\text{qmax}}{\longrightarrow} & D2p + B \\ B + L_{46} & \stackrel{\text{ks}}{\underset{\text{qmax}}{\text{qmax}}} & H_{46} + B_{46} \\ I2n + H_{46} & \stackrel{\text{qmax}}{\longrightarrow} & O_{46} \\ O_{46} + T_{46} & \stackrel{\text{qmax}}{\longrightarrow} & D2pn + B \\ B + L_{47} & \stackrel{\text{ks}}{\underset{\text{qmax}}{\text{qmax}}} & H_{47} + B_{47} \\ I2c + H_{47} & \stackrel{\text{qmax}}{\underset{\text{qmax}}{\text{qmax}}} & D_{2pc} + B \\ \end{split}$$

 $D2c + H_{55} \xrightarrow{q_{\max}} O_{55}$

 $O_{55} + T_{55} \xrightarrow{q_{\text{max}}} M1c + M2nc + sD1p$

$$\begin{array}{cccccccc} O2c+L_{112} & \stackrel{\rm kf}{\overleftarrow{q_{max}}} & H_{112}+B_{112} \\ O2nc+H_{112} & \stackrel{q_{max}}{\frown} & o1_{12} \\ O_{112}+T_{112} & \stackrel{q_{max}}{\frown} & nth \\ \\ M1+L_{113} & \stackrel{\rm kf}{\overleftarrow{q_{max}}} & H_{113}+B_{113} \\ \\ M1n+H_{113} & \stackrel{q_{max}}{\frown} & o1_{13} \\ O_{113}+T_{113} & \stackrel{q_{max}}{\frown} & nth \\ \\ M1c+L_{114} & \stackrel{\rm kf}{\overleftarrow{q_{max}}} & H_{114}+B_{114} \\ \\ M1nc+H_{114} & \stackrel{q_{max}}{\frown} & o1_{14} \\ O_{114}+T_{114} & \stackrel{q_{max}}{\frown} & nth \\ \\ M2c+L_{115} & \stackrel{\rm kf}{\overleftarrow{q_{max}}} & H_{115}+B_{115} \\ \\ M2n+H_{115} & \stackrel{q_{max}}{\frown} & nth \\ \\ M2c+L_{116} & \stackrel{\rm kf}{\overleftarrow{q_{max}}} & H_{116}+B_{116} \\ \\ M2c+L_{116} & \stackrel{\rm kf}{\overleftarrow{q_{max}}} & nth \\ \\ D1+L_{117} & \stackrel{\rm kf}{\overleftarrow{q_{max}}} & nth \\ \\ D1+L_{117} & \stackrel{\rm kf}{\overleftarrow{q_{max}}} & nth \\ \\ D1c+L_{118} & \stackrel{\rm kf}{\overleftarrow{q_{max}}} & H_{118}+B_{118} \\ \\ D1nc+H_{118} & \stackrel{\rm kf}{\overrightarrow{q_{max}}} & nth \\ \\ D2+L_{119} & \stackrel{\rm kf}{\overleftarrow{q_{max}}} & nth \\ \\ D2+L_{119} & \stackrel{\rm kf}{\overleftarrow{q_{max}}} & H_{119}+B_{119} \\ \\ O_{119}+T_{119} & \stackrel{\rm q_{max}}{\rightarrow} & nth \\ \end{array}$$

$$\begin{array}{ccccccccc} D2pc+L_{128} & \stackrel{\rm kf}{\overleftarrow{q_{\rm max}}} & H_{128}+B_{128} \\ D2pnc+H_{128} & \stackrel{\rm q_{\rm max}}{\longrightarrow} & O_{128} \\ O_{128}+T_{128} & \stackrel{\rm q_{\rm max}}{\longrightarrow} & nth \\ D3p+L_{129} & \stackrel{\rm kf}{\overleftarrow{q_{\rm max}}} & H_{129}+B_{129} \\ D3pn+H_{129} & \stackrel{\rm q_{\rm max}}{\longrightarrow} & O_{129} \\ O_{129}+T_{129} & \stackrel{\rm q_{\rm max}}{\longrightarrow} & nth \\ D3pc+L_{130} & \stackrel{\rm kf}{\overleftarrow{q_{\rm max}}} & H_{130}+B_{130} \\ D3pnc+H_{130} & \stackrel{\rm q_{\rm max}}{\longrightarrow} & O_{130} \\ O_{130}+T_{130} & \stackrel{\rm q_{\rm max}}{\longrightarrow} & nth \\ D4p+L_{131} & \stackrel{\rm kf}{\overleftarrow{q_{\rm max}}} & H_{131}+B_{131} \\ D4pn+H_{131} & \stackrel{\rm q_{\rm max}}{\longrightarrow} & nth \\ D4pc+L_{132} & \stackrel{\rm kf}{\overleftarrow{q_{\rm max}}} & nth \\ D4pc+L_{132} & \stackrel{\rm kf}{\overleftarrow{q_{\rm max}}} & H_{132}+B_{132} \\ D4pnc+H_{132} & \stackrel{\rm q_{\rm max}}{\longrightarrow} & nth \\ \end{array}$$

C.4 Binary Counter

$$\begin{array}{rcl} q0+L_1 & \stackrel{\mathrm{kf}}{\underset{\mathrm{qmax}}{\longleftarrow}} & H_1+B_1 \\ R+H_1 & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_1 \\ O_1+T_1 & \stackrel{\mathrm{qmax}}{\longrightarrow} & q0+R+pm1 \\ q1+L_2 & \stackrel{\mathrm{kf}}{\underset{\mathrm{qmax}}{\longleftarrow}} & H_2+B_2 \\ R+H_2 & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_2 \\ O_2+T_2 & \stackrel{\mathrm{qmax}}{\longrightarrow} & q1+R+pm0 \end{array}$$

$$\begin{array}{ccccccccc} pk1 + L_{51} & \stackrel{\rm kf}{\bigoplus} & H_{51} + B_{51} \\ k0 + H_{51} & \stackrel{\rm qmax}{\bigoplus} & O_{51} \\ O_{51} + T_{51} & \stackrel{\rm qmax}{\bigoplus} & k1 \\ k0 + L_{52} & \stackrel{\rm kf}{\bigoplus} & H_{52} + B_{52} \\ k1 + H_{52} & \stackrel{\rm qmax}{\bigoplus} & O_{52} \\ O_{52} + T_{52} & \stackrel{\rm qmax}{\bigoplus} & sk \\ k0 + L_{53} & \stackrel{\rm kf}{\bigoplus} & H_{53} + B_{53} \\ sk + H_{53} & \stackrel{\rm qmax}{\bigoplus} & O_{53} \\ O_{53} + T_{53} & \stackrel{\rm qmax}{\bigoplus} & O_{54} \\ O_{54} + T_{54} & \stackrel{\rm kf}{\bigoplus} & H_{54} + B_{54} \\ sk + H_{54} & \stackrel{\rm kf}{\bigoplus} & H_{55} + B_{55} \\ l1 + H_{55} & \stackrel{\rm qmax}{\bigoplus} & 3k1 \\ l0 + L_{55} & \stackrel{\rm ks}{\bigoplus} & H_{55} + B_{55} \\ l1 + H_{55} & \stackrel{\rm qmax}{\bigoplus} & sl \\ l0 + L_{56} & \stackrel{\rm ks}{\bigoplus} & H_{56} + B_{56} \\ sl + H_{56} & \stackrel{\rm qmax}{\bigoplus} & O_{56} \\ O_{56} + T_{56} & \stackrel{\rm qmax}{\bigoplus} & 3l0 \\ l1 + L_{57} & \stackrel{\rm ks}{\bigoplus} & H_{57} + B_{57} \\ sl + H_{57} & \stackrel{\rm qmax}{\bigoplus} & O_{57} \\ O_{57} + T_{57} & \stackrel{\rm qmax}{\Longrightarrow} & 3l1 \\ f0 + L_{58} & \stackrel{\rm ks}{\bigoplus} & H_{58} + B_{58} \\ f1 + H_{58} & \stackrel{\rm qmax}{\bigoplus} & O_{58} \\ O_{58} + T_{58} & \stackrel{\rm qmax}{\Longrightarrow} & sf \end{array}$$

$$pl1 + L_{83} \quad \stackrel{\text{ks}}{\underset{\text{qmax}}{\longrightarrow}} \quad H_{83} + B_{83}$$

$$pl1 + H_{83} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad O_{83}$$

$$O_{83} + T_{83} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad nth$$

$$pl1 + L_{84} \quad \stackrel{\text{ks}}{\underset{\text{qmax}}{\longrightarrow}} \quad H_{84} + B_{84}$$

$$l0 + H_{84} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad O_{84}$$

$$O_{84} + T_{84} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad l1$$

C.5 Linear Feedback Shift Register
$$px0 + L_{62} \quad \stackrel{\text{kf}}{\underset{\text{qmax}}{\text{qmax}}} \quad H_{62} + B_{62}$$

$$px0 + H_{62} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad O_{62}$$

$$O_{62} + T_{62} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad nth$$

$$px1 + L_{63} \quad \stackrel{\text{kf}}{\underset{\text{qmax}}{\text{max}}} \quad H_{63} + B_{63}$$

$$px1 + H_{63} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad O_{63}$$

$$O_{63} + T_{63} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad nth$$

$$px0 + L_{64} \quad \stackrel{\text{kf}}{\underset{\text{qmax}}{\text{qmax}}} \quad H_{64} + B_{64}$$

$$x1 + H_{64} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad O_{64}$$

$$O_{64} + T_{64} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad x0$$

$$px1 + L_{65} \quad \stackrel{\text{kf}}{\underset{\text{qmax}}{\text{qmax}}} \quad H_{65} + B_{65}$$

$$x0 + H_{65} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad O_{65}$$

$$O_{65} + T_{65} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad x1$$

C.6 Square Root Unit

$$\begin{array}{ccccc} v10+L_1 & \stackrel{k}{\overleftarrow{q_{\max}}} & H_1+B_1 \\ v10+H_1 & \stackrel{q_{\max}}{\longrightarrow} & O_1 \\ O_1+T_1 & \stackrel{q_{\max}}{\longrightarrow} & v10+v10+pdd10 \\ v11+L_2 & \stackrel{k}{\overleftarrow{q_{\max}}} & H_2+B_2 \\ v10+H_2 & \stackrel{q_{\max}}{\longrightarrow} & O_2 \\ O_2+T_2 & \stackrel{q_{\max}}{\longrightarrow} & v11+v10+pdd11 \\ v11+L_3 & \stackrel{k}{\overleftarrow{q_{\max}}} & H_3+B_3 \\ v11+H_3 & \stackrel{q_{\max}}{\longrightarrow} & O_3 \\ O_3+T_3 & \stackrel{q_{\max}}{\longrightarrow} & v11+v11+pdd10 \end{array}$$

$$poa10 + L_{27} \quad \stackrel{k}{\underset{\text{qmax}}{\longrightarrow}} \quad H_{27} + B_{27}$$
$$poa10 + H_{27} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad O_{27}$$
$$O_{27} + T_{27} \quad \stackrel{\text{qmax}}{\longrightarrow} \quad nth$$

$$boa20 + L_{83} \quad \stackrel{\mathsf{K}}{\underset{q_{\max}}{\longleftarrow}} \quad H_{83} + B_{83}$$
$$oa21 + H_{83} \quad \stackrel{q_{\max}}{\longrightarrow} \quad O_{83}$$
$$O_{83} + T_{83} \quad \stackrel{q_{\max}}{\longrightarrow} \quad oa20$$

$$\begin{aligned} dd30 + L_{131} & \stackrel{\mathbf{k}}{\underset{\mathbf{q}_{\max}}{\longleftarrow}} & H_{131} + B_{131} \\ a41 + H_{131} & \stackrel{\mathbf{q}_{\max}}{\longrightarrow} & O_{131} \\ O_{131} + T_{131} & \stackrel{\mathbf{q}_{\max}}{\longrightarrow} & dd30 + a41 + pxa31 \end{aligned}$$

 $O_{177} + T_{177} \xrightarrow{q_{\text{max}}} oa40 + ac40 + pc210$

$$\begin{array}{cccc} pc210+L_{178} & \stackrel{\mathrm{k}}{\underset{\mathrm{qmax}}{\overset{\mathrm{max}}{\longrightarrow}}} & H_{178}+B_{178} \\ pc210+H_{178} & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_{178} \\ O_{178}+T_{178} & \stackrel{\mathrm{qmax}}{\longrightarrow} & nth \\ pc210+L_{179} & \stackrel{\mathrm{k}}{\underset{\mathrm{qmax}}{\overset{\mathrm{max}}{\longrightarrow}}} & H_{179}+B_{179} \\ c211+H_{179} & \stackrel{\mathrm{qmax}}{\longrightarrow} & O_{179} \\ O_{179}+T_{179} & \stackrel{\mathrm{qmax}}{\longrightarrow} & c210 \end{array}$$

 $O_{187} + T_{187} \xrightarrow{q_{\max}} nth$

 $O_{203} + T_{203} \stackrel{\text{qmax}}{\longrightarrow} q31 + q30 + pdd51$

$$\begin{array}{cccc} pdd60 + H_{242} & \stackrel{\text{qmax}}{\longrightarrow} & O_{242} \\ O_{242} + T_{242} & \stackrel{\text{qmax}}{\longrightarrow} & nth \\ pdd61 + L_{243} & \stackrel{k}{\underset{\text{qmax}}{\longleftarrow}} & H_{243} + B_{24} \\ pdd61 + H_{243} & \stackrel{\text{qmax}}{\longrightarrow} & O_{243} \\ O_{243} + T_{243} & \stackrel{\text{qmax}}{\longrightarrow} & nth \end{array}$$
$$\begin{array}{rcl} a20 + H_{274} & \xrightarrow{\text{Image}} & O_{274} \\ O_{274} + T_{274} & \xrightarrow{\text{qmax}} & dd60 + a20 + pxa60 \\ dd61 + L_{275} & \xrightarrow{\text{k}} & H_{275} + B_{275} \\ a20 + H_{275} & \xrightarrow{\text{qmax}} & O_{275} \\ O_{275} + T_{275} & \xrightarrow{\text{qmax}} & dd61 + a20 + pxa61 \end{array}$$

 $O_{283} + T_{283} \xrightarrow{q_{\text{max}}} xa61 + q20 + pr001$

 $O_{339} + T_{339} \xrightarrow{q_{\text{max}}} xa71 + c101 + pr010$

$$O_{368} + T_{368} \quad \stackrel{\mathbf{q}_{\max}}{\longrightarrow} \quad c111 + r101 + pac81$$

$$pac81 + L_{369} \xrightarrow{k} H_{369} + B_{369}$$

$$pac81 + H_{369} \xrightarrow{q_{max}} O_{369}$$

$$O_{369} + T_{369} \xrightarrow{q_{max}} nth$$

$$pac81 + L_{370} \xrightarrow{k} H_{370} + B_{370}$$

$$ac80 + H_{370} \xrightarrow{q_{max}} O_{370}$$

$$O_{370} + T_{370} \xrightarrow{q_{max}} ac81$$

$$aa81 + L_{371} \xrightarrow{k} H_{371} + B_{371}$$

$$oa80 + H_{371} \xrightarrow{q_{max}} O_{371}$$

 $\stackrel{q_{\max}}{\longrightarrow}$ $O_{371} + T_{371}$ aa81 + oa81

$$\begin{array}{rrrr} r101 + H_{386} & \stackrel{q_{\max}}{\longrightarrow} & O_{386} \\ O_{386} + T_{386} & \stackrel{q_{\max}}{\longrightarrow} & dd81 + r101 + pxa80 \\ dd80 + L_{387} & \stackrel{k}{\underset{q_{\max}}{\longleftarrow}} & H_{387} + B_{387} \end{array}$$

 $r101 + H_{387} \xrightarrow{q_{\text{max}}} O_{387}$

 $O_{387} + T_{387} \quad \stackrel{\mathbf{q}_{\max}}{\longrightarrow} \quad dd80 + r101 + pxa81$

$$\begin{array}{ccc} pq10+L_{435} & \stackrel{\mathbf{k}}{\underset{\mathbf{q}_{\mathrm{max}}}{\longleftarrow}} & H_{435}+B_{435} \\ q11+H_{435} & \stackrel{\mathbf{q}_{\mathrm{max}}}{\longrightarrow} & O_{435} \\ O_{435}+T_{435} & \stackrel{\mathbf{q}_{\mathrm{max}}}{\longrightarrow} & q10 \end{array}$$

nth

$$paa121 + L_{523} \qquad \stackrel{k}{\underset{q_{max}}{\longleftarrow}} \qquad H_{523} + B_{523}$$
$$aa120 + H_{523} \qquad \stackrel{q_{max}}{\longrightarrow} \qquad O_{523}$$
$$O_{523} + T_{523} \qquad \stackrel{q_{max}}{\longrightarrow} \qquad aa121$$
$$paa141 + L_{595} \quad \stackrel{k}{\underset{q_{max}}{\longleftarrow}} \quad H_{595} + B_{595}$$
$$aa140 + H_{595} \quad \stackrel{q_{max}}{\longrightarrow} \quad O_{595}$$
$$O_{595} + T_{595} \quad \stackrel{q_{max}}{\longrightarrow} \quad aa141$$