A Poisson Process Generator Based on Multiple Thermal Noise Amplifiers for Parallel Stochastic Simulation of Biochemical Reactions

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Abstract: In this paper, we propose a novel Poisson process generator that uses multiple thermal noise amplifiers (TNAs) as a source of randomness and controls its event rate via a frequency-locked loop (FLL). The increase in the number of TNAs extends the effective bandwidth of amplified thermal noise and hence enhances the maximum event rate the proposed architecture can generate. Verilog-A simulation of the proposed Poisson process generator shows that its maximum event rate can be increased by a factor of 26.5 when the number of TNAs increases from 1 to 10. In order to realize parallel stochastic simulations of the biochemical reaction network, we present a fundamental reaction building block with continuous-time multiplication and addition using an AND gate and a 1-bit current-steering digital-to-analog converter, respectively. Stochastic biochemical reactions consisting of the fundamental reaction building blocks are simulated in Verilog-A, demonstrating that the simulation results are consistent with those of conventional Gillespie algorithm. An increase in the number of TNAs to accelerate the Poisson events and the use of digital AND gates for robust reaction rate calculations allow for faster and more accurate stochastic simulations of biochemical reactions than previous parallel stochastic simulators.

Keywords: Poisson process generator; thermal noise amplifier; AND gate; stochastic simulation; biochemical reactions

1. Introduction

As cells often process signals with a low or medium number of molecules and exploit the stochasticity in their cellular functions [1–5], the stochastic simulation of biochemical reaction networks is essential in systems and computational biology. Although the Gillespie algorithm [6] and its variants [7–13] have been presented for the software simulation of stochastic biochemical reactions, there is a problem where the simulation time increases proportionally as the size of the biochemical reaction network increases. This is because of the intrinsic limitation of software simulation that cannot process the correlated stochastic reactions in parallel.

There have been several attempts to implement hardware specialized for parallel simulation of stochastic biochemical reactions in order to solve the problem of long simulation times in software [14–24]. Ref. [14] presented a field-programmable gate array (FPGA)-based parallel stochastic simulator by comparing random numbers with the number of molecules of each reactant and performing a logic AND operation on the comparators’ outputs. However, pseudo-random number generators that are not truly random were used, and the reaction events with a time interval within one clock cycle cannot be simulated. In [15–17], BiCMOS cytomorphic chips based on log-domain analog circuits were
presented for continuous-time parallel stochastic simulation. Although random pulses generated with amplified thermal noise were incorporated into the core transistor circuits for modeling high intrinsic noise levels [16], stochastic simulation of reactions with a few molecules was unfeasible. This is because the random pulses corresponding to Poisson events have different widths each time, making it difficult to count the molecules accurately.

In this paper, we propose a novel Poisson process generator that uses multiple thermal noise amplifiers (TNAs) as the random source and controls its event rate via a frequency-locked loop (FLL). Unlike the previous work in [16], the use of multiple TNAs enables the Poisson process generator to enhance its maximum event rate by extending the effective bandwidth of amplified thermal noise. In addition, a pulse-width equalizer is included to precisely map each output pulse to a single molecular event. For parallel stochastic simulation of biochemical reactions, we also propose a fundamental reaction building block with an AND gate and a current-steering DAC. Advantageously, the calculation of reaction rates using such asynchronous time-based circuits can achieve higher accuracy than the conventional analog calculation based on translinear circuits. It also enables digital routing between fundamental reaction building blocks without using analog-to-digital converters that were used for routing between chips in [15,17].

This paper is organized as follows: Section 2 describes the operation principle of the proposed Poisson process generator and the effect of increasing the number of thermal noise amplifiers. Next, Section 3 introduces the architecture in which the event rate of the Poisson process is determined by the continuous-time multiplication using an AND gate. Section 4 presents the fundamental reaction building block for parallel stochastic simulation of biochemical reactions. Then, Section 5 provides Verilog-A simulation results of bidirectional second order reactions and amyloid-beta turnover in Alzheimer’s disease that show good agreement with those of the Gillespie algorithm. Finally, Section 6 summarizes our main conclusions.

2. Proposed Poisson Process Generator

2.1. Operation Principle

The architecture and the operation of the proposed Poisson process generator are shown in Figures 1a and 1b, respectively, where the number of thermal noise amplifiers (TNAs) is 2 in Figure 1b. N number of TNAs provide N amplified thermal noises that are independently and identically distributed. Note that the TNA can be implemented with cascaded common source amplifier stages and a large dominant pole capacitor at the output node of the first stage [16]. Furthermore, N comparators generate pulses corresponding to Poisson events whenever each amplified thermal noise becomes lower than a common threshold voltage \( V_{th}(t) \). A pulse width equalizer based on a D flip-flop produces Poisson events with the same pulse width. As shown in Figure 1a, the event rate of the Poisson process is controlled through an FLL which compares and matches it with the VCO output frequency set by the input voltage \( V_{\lambda}(t) \). The XOR logic gate generates a high only in an odd number of high inputs and collects N parallel Poisson pulses into one signal. In order to compare the frequency of the VCO output with a duty cycle of 0.5, the XOR output is divided by two in the frequency domain [16]. When the VCO gain and offset frequency are \( K_{VCO} \) and \( f_{os} \), respectively, the mean frequency of each output channel of the proposed Poisson process generator (\( f_{PPG}(t) \)) is as follows.

\[
f_{PPG}(t) = \frac{2(K_{VCO}V_{\lambda}(t) + f_{os})}{N}
\]
2.2. Effect of Increasing $N$

The Poisson process is best understood intuitively as a continuous-time analog of the Bernoulli process. Moreover, the success in a Bernoulli trial corresponds to the transition in which the output of the TNA is higher than the threshold voltage $V_{th}(t)$ and then lowered in the proposed Poisson process generator (Figure 1a). Moreover, the consecutive success in Bernoulli trials corresponds to the case where the TNA output becomes lower than the threshold voltage for a period as long as a multiple of its bandwidth reciprocal. In this case, the problem is that the proposed Poisson process generator produces only one pulse, not multiple pulses corresponding to consecutive successes. By placing the threshold voltage away from the mean of amplified thermal noise, the probability of consecutive successes can be reduced. However, it lowers the maximum rate that the proposed architecture can generate, slowing down the stochastic simulation of biochemical reactions that will be described in Section 4.

The maximum event rate of the proposed Poisson process generator can be improved by increasing the number of thermal noise amplifiers, $N$, in Figure 1a. Assuming that the amplified thermal noises obtained from $N$ number of TNAs are independent, the effective bandwidth of amplified thermal noise is extended by a factor of $N$, and hence the rate of Poisson events increases in proportion to $N$. In order to verify the improvement of the event rate by increasing $N$, the Poisson process generation in Figure 1a was simulated using
Verilog-A. Note that the bandwidth of amplified thermal noise was set to 160 MHz in the simulation. Figure 2 shows the simulated time-interval histograms of N-channel outputs when N is 1 and 10, respectively. For each N, it also shows the simulation results when the threshold voltage \( V_{th} \) is the mean of the amplified thermal noise \( \mu_{VTNA} \) and as low as 1.5 times its standard deviation \( 1.5 \sigma_{VTNA} \) from the mean, respectively.

**Figure 2.** (a) Simulated time-interval histograms of the Poisson process generation in Figure 1a. (b) \( N = 1, V_{th}(t) = \mu_{VTNA} \), mean event rate = 38.02 MHz. (c) \( N = 1, V_{th}(t) = \mu_{VTNA} - 1.5 \sigma_{VTNA} \), mean event rate = 14.4 MHz. (d) \( N = 10, V_{th}(t) = \mu_{VTNA} - 1.5 \sigma_{VTNA} \), mean event rate = 142.4 MHz. (e) \( N = 10, V_{th}(t) = \mu_{VTNA} \), mean event rate = 382 MHz.

Figure 2b shows a time-interval histogram, the simulated statistics of the inter-event rate vs. time, when \( N = 1 \) and \( V_{th} \) is \( \mu_{VTNA} \). Note that the mean event rate of the simulated Poisson process is 38.02 MHz. When \( V_{th} \) is located at \( \mu_{VTNA} \), the probability of success, the transition in which the output of the TNA is higher than \( V_{th} \) and then lowered, is 0.5. Therefore, an ideal time-interval histogram should follow the exponential distribution with the mean event rate of 80 MHz. However, since the proposed Poisson process generator recognizes the consecutive successes that occur frequently at \( V_{th} = \mu_{VTNA} \), as only one success, the simulated mean event rate is reduced to 38.02 MHz. In addition, as shown in
Figure 2b, it can be seen that the simulated time interval histogram does not follow the exponential distribution indicated by the red line, severely lacking events with relatively short time intervals.

Figure 2c shows a simulated time-interval histogram with $N = 1$ and $V_{th} = \mu_{VTNA} - 1.5 \sigma_{VTNA}$, where the mean event rate of the simulated Poisson process is 14.4 MHz. Although the simulated mean event rate is decreased by a factor of 2.64 than that of Figure 2b, the simulated time-interval histogram follows the exponential distribution well by placing $V_{th}$ as far away from $\mu_{VTNA}$ as $1.5 \sigma_{VTNA}$ to reduce the probability of consecutive successes. Figure 2d shows a simulated time-interval histogram with $N = 10$ and $V_{th} = \mu_{VTNA} - 1.5 \sigma_{VTNA}$. It can be seen that the simulated histogram is in good agreement with an exponential distribution as the probability of consecutive successes is low as shown in Figure 2c. The mean event rate of the simulated Poisson process is 142.4 MHz, which is 9.87 times higher than that of Figure 2c. This is because the effective bandwidth that the amplified thermal noise is extended with is in proportion to 10, the number of TNAs in Figure 2d.

Figure 2e shows a simulated time-interval histogram with $N = 10$ and $V_{th} = \mu_{VTNA}$, where the mean event rate of the simulated Poisson process is 382 MHz. Interestingly, the simulated histogram still follows an exponential distribution even when the threshold voltage is $\mu_{VTNA}$. This is because short time intervals that were insufficient in Figure 2b due to the omission of consecutive success are filled with those produced by serializing parallel Poisson events obtained from 10 TNAs. Therefore, increasing $N$ in the proposed Poisson process generator provides an additional acceleration that can be achieved by placing the threshold voltage close to $\mu_{VTNA}$. From Figure 2c,e, when $N$ is increased by a factor of 10, it can be observed that the maximum event rate of the proposed Poisson process generator is increased by a factor of 26.5.

3. Stochastic Multiplication Using AND Gate

According to the law of mass action, the rate of a chemical reaction is proportional to the product of the reactant concentrations. It is necessary to implement the multiplication of the concentration of the reactants and a reaction constant to apply the proposed Poisson process generator described in Section 2 to the stochastic simulation of biochemical reactions. As shown in Figure 3a, the multiplication is performed first, and the result can be applied as an input to the Poisson process generator. However, analog multipliers, including a translinear current-mode circuit [15–17], are difficult to achieve with high accuracy due to device mismatch, PVT variations, and limited dynamic range.

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**Figure 3.** Block diagram of Poisson process generation in which the event rate is determined by (a) conventional analog multiplication and (b) proposed stochastic multiplication of logic AND gate.
In order to alleviate this problem, we propose the Poisson process generation in which the event rate is determined by the stochastic multiplication of digital logic AND gates, as shown in Figure 3b. The output pulse from one of the three Poisson process generators in Figure 3b passes through the AND gate only when the outputs of the other two Poisson process generators are both HIGH. Therefore, the mean frequency of the AND gate output can be obtained as

$$\lambda_{\text{AND}}(t) = f_{\text{PPG}1}(t)P_{\text{high}2}(t)P_{\text{high}3}(t) + f_{\text{PPG}2}(t)P_{\text{high}1}(t)P_{\text{high}3}(t) + f_{\text{PPG}3}(t)P_{\text{high}1}(t)P_{\text{high}2}(t)$$

(2)

where $f_{\text{PPG}i}$ is the mean frequency of each output channel of the Poisson process generator that receives $V_{\lambda i}(t)$ as an input voltage. $P_{\text{high}i}$ is the probability that the output of the $i$-th Poisson process generator is HIGH, and can be represented as

$$P_{\text{high}i}(t) = f_{\text{PPG}i}(t)\tau_{\text{PW}}$$

(3)

where $\tau_{\text{PW}}$ is the width of the output pulse of the Poisson process generator. In order to treat each pulse from the AND gates as an occurrence of the Poisson event, their widths are equalized via the pulse width equalizers. By applying (3) to (2), the output rate of the proposed architecture in Figure 3b, the mean rate of the Poisson events obtained from the outputs of $N$ channel AND gates, can be obtained as the following equation.

$$\lambda_{\text{OUT}}(t) = N f_{\text{PPG}1}(t)f_{\text{PPG}2}(t)f_{\text{PPG}3}(t)(3\tau_{\text{PW}}^2)$$

(4)

The time-interval histogram obtained by simulating the proposed architecture of Figure 3b in Verilog-A is shown in Figure 4. Note that the Poisson process generators transmitting their outputs to the AND gates are all set to the same condition as the simulation in Figure 2e, where $N$ is 10, $f_{\text{PPS}}$ is 38.2 MHz and $\tau_{\text{PW}}$ is 6.25 ns. It can be seen that the simulated histogram follows the exponential distribution well even after passing through the AND gate. The simulated mean frequency of the output Poisson events is 67.9 MHz, which is close to the theoretical value of 75 MHz from (4). The difference between the simulated frequency and the theoretical value arises from the nonzero setup time of the pulse width equalizer where the output pulses of the AND gate with a width shorter than the setup time are omitted.

Figure 4. Time-interval histograms of the simulated output of Figure 3b.
4. Fundamental Reaction Building Block

Figure 5 shows the fundamental reaction building block for the stochastic simulation of association reaction \( A + B \rightarrow C \) and dissociation reaction \( C \rightarrow B + A \), where \( K_a \) and \( K_d \) are its reaction constant, respectively. \( V_{[A]}, V_{[B]}, \) and \( V_{[C]} \) represent the voltage corresponding to the concentrations of reactant \( A, B, \) and \( C \), respectively. Moreover, \( V_{ka} \) and \( V_{kd} \) denote the voltage corresponding to the reaction constant \( K_a \) and \( K_d \), respectively. Additionally, \( V_{[I]} \) is the voltage at which the reactant concentration is 1. Stochastic events of the association reaction and the dissociation reaction with a rate of \( K_a[A][B] \) and \( K_d[C] \), respectively, are generated from the proposed architecture of Figure 3b. \( V_{[I]}, V_{[B]}, \) and \( V_{[C]} \) are updated by 1-bit current-steering digital-to-analog converters (DACs) shown in Figure 5. Since the reaction order of the dissociation reaction is less than that of the association reaction by 1, \( V_{[I]} \) is applied to the input of the Poisson process generator that does not have a corresponding input.

![Diagram of the fundamental reaction building block](image)

Figure 5. Fundamental reaction building block for stochastic simulation of bidirectional second-order reaction: \( A + B \leftrightarrow C \).

From (1) and (4), the mean rate of association reaction (\( \lambda_a \)) and the mean rate of dissociation reaction (\( \lambda_d \)) can be obtained as follows

\[
\lambda_a = \frac{24K_{VCO}V_{[I]}^3\tau_{PW}^2}{N^2}K_a[A][B]
\]  

(5)
where the offset frequency of the VCO is assumed to be much less than the oscillation frequency [25]. Consequently, the simulation speed of the proposed fundamental reaction building block is scaled by $24K_{\text{VCO}}V[1]^3\tau_{\text{PW}}^2/N^2$ than the actual biochemical reaction rate. The upper limit of $V[1]$ to be maximized for fast simulation is determined by the maximum event rate that the proposed Poisson process generator of Figure 1a can produce. As discussed in Section 2, it can be increased proportionally when $N$ is small and even more than that when $N$ approaches 10.

When a large-scale biochemical reaction network is constructed using the proposed architecture in Figure 5, the routing between reaction building blocks is achieved via asynchronous digital pulses corresponding to the event stream of the Poisson process. Thus, unlike the previous works that use analog-to-digital converters for routing between chips [15–17], it has the advantage of implementing the large-scale stochastic biochemical reaction network without errors due to synchronization or quantization.

5. Stochastic Simulation Results of Biochemical Reactions

Gillespie stochastic simulation results from COPASI [26] and Verilog-A simulation results of Figure 5 for the bidirectional second-order reaction ($A + B \leftrightarrow C$ and $C \rightarrow A + B$) are shown in Figure 6a,b, respectively, where $K_a = 80$, $K_d = 800$, and the initial value of $[A]$, $[B]$, and $[C]$ is 600, 400, and 0. In the simulation presented in Figure 5, $V[1]$ was 5 mV, the output pulse width of pulse width equalizers was 5 ns, and the output current of current sources in the current steering DAC was 100 µA. For each Poisson process generator, $N$ was set to 5, $K_{\text{VCO}}$ was set to 25 MHz/V, and the TNA bandwidth was set to 200 MHz. In addition, a second-order passive loop filter with two 1 pF capacitors and one 860 kΩ resistor was used in the FLL. From (5) and (6), the simulated reaction rates of Figure 6b are scaled up by 21 than the actual biochemical reaction rates. It can be seen that the simulation results of Figure 5 are in good agreement with those of conventional Gillespie’s algorithm.

![Figure 6](image_url)

**Figure 6.** Simulation results of (a) Gillespie stochastic algorithm and (b) the proposed architecture of Figure 5 for the reactions: $A + B \leftrightarrow C$. Note that the simulated reaction rates of (b) are scaled up by 21 than the actual biochemical reaction rates.

In order to verify the stochastic simulation of very-low-molecule-number biochemical reactions that were not feasible in [16], we simulated the following stochastic model of amyloid-beta (Aβ) turnover [27], which is widely used in research studies for Alzheimer’s disease.

$$\text{Source} \xrightarrow{K_{\text{prod}}} \text{Aβ} \xrightarrow{K_{\text{deg}}} \text{Sink} \quad (7)$$
Due to a slight decrease in $K_{\text{deg}}$, the number of $\text{A}\beta$ molecules can exceed a normal basal level (four in [27]) for short periods of time, and it may cause dimerization of $\text{A}\beta$ monomers, which can initiate the aggregation process of Alzheimer’s disease.

Figure 7 shows an architecture based on the proposed fundamental reaction building block of Figure 5 for the stochastic simulation of $\text{A}\beta$ turnover in (7). Since (7) consists of a zero-order association reaction and a first-order dissociation reaction, only two Poisson process generators are required for the AND gate-based stochastic multiplication.

**Figure 7.** Fundamental reaction building block for stochastic simulation of the model of amyloid beta ($\text{A}\beta$) turnover.

Gillespie stochastic simulation results of $\text{A}\beta$ turnover in (7) are shown in Figure 8a where $K_{\text{prod}} = 1.86 \times 10^{-5}$ molecules/s and $K_{\text{deg}} = 1.5 \times 10^{-5}$ molecules/s. In order to examine the aggregation process of Alzheimer’s disease in human aging, the simulated time is set to 100 years [27]. The mean and the standard deviation of the simulated number of reactant $\text{A}\beta$ ([Aβ]) are 1.296 and 1.159, respectively. Verilog-A simulation results of Figure 7 are shown in Figure 8b where the simulation parameters are set to $N = 10$, $V_{\text{H}} = 5$ mV, $\tau_{\text{PW}} = 5$ ns, and $K_{\text{VCO}} = 50$ MHz/V, scaling the simulated reaction rates by $3.125 \times 10^9$ than the actual biochemical reaction rates. It can be seen that the time taken for 100 years in actual biochemical reactions is shortened to 3.5 ms in Figure 8b. The mean and the standard deviation of the simulated [Aβ] are 1.301 and 1.18, respectively. Figure 8 indicates that the simulation based on the proposed fundamental reaction building blocks is consistent with the Gillespie stochastic simulation, even in the biochemical reactions with very few molecules.
Figure 8. Simulation results of (a) Gillespie stochastic algorithm and (b) the architecture of Figure 7 for the reactions of Aβ turnover. Note that the simulated reaction rates of (b) are scaled up by $3.125 \times 10^9$ than the actual biochemical reaction rates.

6. Conclusions

In this work, we presented a multiple TNAs-based Poisson process generator and fundamental reaction building blocks for parallel stochastic simulation of biochemical reactions. Increasing the number of TNAs to accelerate the Poisson events and employing digital AND gates for robust reaction rate calculations allow for faster and more accurate stochastic simulations of biochemical reactions than previous parallel stochastic simulators.

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