Effect of Molecular Noise on the Dynamics of Tryptophan Operon System in *Escherichia coli*

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EXTENDED ABSTRACT

Noise in gene expression, or the variation in gene expression in an isogenic population under a homogeneous environment, has been of much interest in recent years. Differences in gene expression of two isogenic cells could be attributed to the variation in factors determining gene expression in these cells, such as transcription factors, the concentration of operators, RNA polymerase, the cell cycle, etc., which is termed extrinsic noise. However, variation could still persist even when all extrinsic noise is eliminated, due to the limited number of molecules for typical molecular species involved. The latter is termed intrinsic noise. It has been shown theoretically and confirmed experimentally that stochasticity is an inherent feature of gene expression (Arkin et al., 1998; Blake et al., 2003; Elowitz et al., 2002; Rao et al., 2002), and that these random fluctuations may play important roles in cellular processes (Turner et al., 2004). However, the implications of stochastic gene expression are still not clear. There is very little knowledge about the consequences of stochasticity on particular systems.

Because of the complexity of genetic regulatory networks, where non-linear interactions between components are commonplace, many mathematical models have been developed to obtain insights into the dynamical features of the networks. Most of these models are of a deterministic nature and take the form of coupled ordinary differential equations. However, the question arises as to whether deterministic models are always appropriate for the description of genetic networks. This is because in genetic networks, many intracellular components are present at very low quantities: the gene copy number is typically one or two; and the number of transcriptional factors is frequently in order of tens (Ramanathan & Swain, 2005). At such low concentration it becomes necessary to resort to stochastic approaches. Only by using stochastic modelling can we study the effect of noise on the dynamics of systems. Stochastic modelling enables us to discover system behaviours which might have been neglected in deterministic descriptions.

Here, we seek to better understand what differences may result from stochastic and deterministic kinetic approaches to modelling genetic regulatory systems by considering a model system of tryptophan (Trp) operon system in *Escherichia coli*. This genetic regulatory network is responsible for the production of tryptophan amino acid inside the cells. The molecular basis of the system is presented in the introduction part of the paper. The development and analysis of two stochastic models for the tryptophan operon system are discussed in section 2 and 3. In the first model we introduce molecular noise by setting up stochastic differential equations using the Langevin approach in which molecular fluctuation in the form of white noise is explicitly considered. The second stochastic model is based on the Gillespie method. Due to the lack of data on kinetic rates for elementary reaction steps of molecular processes, the implementation of the Gillespie method is carried out without decomposing the deterministic mechanism into detailed reaction steps. Simulation results from two versions of the stochastic regimes are compared to their deterministic counterpart.

We found that intrinsic fluctuations resulted from molecular noise can destroy stable oscillatory behaviour. In this case, a new value for the bifurcation point is established, which is far from the corresponding deterministic bifurcation point. Moreover, we demonstrate that intrinsic noise can enable the system to obtain qualitatively different dynamics compared to when noise is absent. Specifically, stable sustained oscillations are obtained only when molecular noise is incorporated. Quantification of noise strength for key molecular species indicates that the transcription process exhibits high fluctuation levels which subsequently suggests that in order to reduce noise at the tryptophan output level, one may consider speeding up *mRNA* transcripts degradation.

1. INTRODUCTION

We consider the tryptophan operon system in *Escherichia coli* as the model system to study the effect of molecular noise on system's dynamics in comparison to when noise is absent; and to quantify fluctuations in the abundance of different molecular components under the influence of noise.

The tryptophan operon system controls the production of tryptophan amino acid inside the cell. Key molecular processes include transcription, translation and synthesis of tryptophan. To regulate these processes, the tryptophan operon utilises three negative feedback mechanisms: transcriptional repression, attenuation, and enzyme inhibition (Yanofsky, 2003). The transcription process is initiated as RNA polymerase binds to the promoter. However, when the activated form of repressor which is induced by the attachment of two tryptophan molecules become abundant, it will bind to the operator site and block RNA polymerase from binding to the promoter, thereby, repressing transcription and forming the first feedback loop. Furthermore, transcription can also be attenuated depending on the level of intracellular tryptophan and is controlled by the leader region sitting between the operator and the genes (Figure 1). This attenuation makes up the second feedback loop. The tryptophan operon consists of five structural genes positioned consecutively after the leader region. These genes code for five polypeptides that make up enzyme molecules in the form of tetramers, which in turn catalyse the synthesis of tryptophan from chorismates (Santillan & Mackey, 2001; Yanofsky, 2003). Anthranilate synthase (AS) is the enzyme catalysing the first reaction step in the tryptophan synthesis pathway. The pathway end product tryptophan is fedback to inhibit anthranilate synthase activity if tryptophan level is high. Enzyme inhibition therefore forms the third negative feedback loop in the tryptophan operon system.

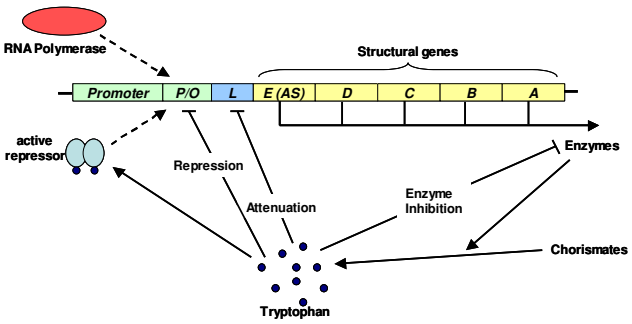

Figure 1. Schematic diagram of the tryptophan operon system. 5 genes are denoted as E (AS), D, C, B and A. P, O, L denotes the promoter, operator and leader region, respectively. Blunt arrow represents inhibition while normal arrow represents activation.

2. DEVELOPMENT OF STOCHASTIC MODELS

To assess the effect of molecular noise we describe two stochastic versions of the tryptophan operon system using two predominantly used frameworks in stochastic modelling of biochemical reactions: stochastic differential equations (Langevin equations) and stochastic simulation algorithm (Gillespie's SSA).

2.1. Derivation of the Langevin Equations

In this section, we firstly describe the theoretical derivation of the Langevin equations following Gillespie's argument (Gillespie, 2000). Let us consider a biochemical system of N molecular species $\{S_1, S_2,\ldots, S_N\}$ that interact chemically through M reaction channels $\{R_1, R_2,\ldots, R_M\}$, where $N, M \geq 1$. Let $v=\{v_{ji}\}$, $j=1,..,M$; $i=1,..,N$ be the stoichiometric matrix of the system. The system's state at the current time t can be represented as $x(t) = (x_1(t), x_2(t),\ldots, x_N(t))$ where $x_i(t)$ is the number of S_i molecules in the system at time t. For each reaction channel R_j and for any time difference $\tau>0$, denote a random variable $K_j(x(t), \tau)$ as the number of reactions of channel R_j that occur in the subsequent time interval $[t,t+\tau]$. Since each of these reactions will change the S_i population by v_{ji}, the number of S_i molecules in the system at time $t+\tau$ will be:

$$x_i(t+\tau) = x_i(t) + \sum_{j=1}^{M} v_{ji}\, K_j(x(t),\tau) \quad (i=1,...,N). \quad (1)$$

An excellent approximation to $K_i(x(t), \tau)$ in equations (1) can be obtained by imposing two conditions on τ (Gillespie, 2000): (i) τ is small enough so that the propensity functions $r_j(x(t))$ $(j=1,..,M)$ for all reactions vary little during the period $[t,t+\tau]$ and each $K_j(x(t), \tau)$ will therefore be a statistically independent Poisson random variable $P_j(r_j(x(t)), \tau)$:

$$K_j(x(t),\tau) = P_j(r_j(x(t)),\tau) \quad (j=1,...,M). \quad (2)$$

(ii) τ is large enough so that the expected number of occurrences of each reaction channel R_j in $[t,t+\tau]$ be much larger than 1, which allows us to approximate each statistically independent Poisson random variable $P_j(r_j(x(t)), \tau)$ by a normal random variable $N_j(m_j, \sigma_j^2)$ with the same mean $m_j = r_j(x(t))\tau$ and variance $\sigma_j^2 = r_j(x(t))\tau$; then,

$$P_j(r_j(x(t)),\tau) = N_j(r_j(x(t))\tau, r_j(x(t))\tau)\,. \quad (3)$$

Using $N(m,\sigma^2) = m + \sigma N(0,1)$, where $N(0,1)$ is the unit normal random variable, equation (1) now become (Gillespie, 2000; Turner et al., 2004):

$$dx_i(t) = \sum_{j=1}^{M} v_{ji} r_j(x(t))dt + \sum_{j=1}^{M} v_{ji}\sqrt{r_j(x(t))}dW_j(t) \quad (4)$$

for i=1,..,N. $dW_{j=1,....,M}(t)$ are M independent Wiener processes associated with the M reaction channels, with $\langle dW_j(t)\rangle = 0$ and $\langle dW_j(t)dW_j(t')\rangle = \delta_{ij}\delta(t-t')$. Equation (4) has the canonical form of standard Langevin equations for multivariate continuous Markov processes.

By relating the concentration of species $X_i(t)$ and the number of molecules $x_i(t)$ using $X_i(t) = x_i(t)/\Omega$, where Ω is the total cell volume, we can obtain the chemical Langevin equations in the form of species concentrations:

$$dX_i(t) = \sum_{j=1}^{M} v_{ji} r_j(X(t))dt + \frac{1}{\sqrt{\Omega}}\sum_{j=1}^{M} v_{ji}\sqrt{r_j(X(t))}dW_j(t) \quad (5)$$

It can be noted that the internal fluctuation term is proportional to $\eta = 1/\sqrt{\Omega}$ in equation (5). In the macroscopic limit $\Omega \to \infty$; $\eta \to 0$ and the internal noise terms can be ignored, resulting in the deterministic dynamics.

Returning to the Trp operon system presented in section 1, we identified four key molecular species which are free operator, mRNA, enzyme, and intracellular tryptophan with corresponding concentrations denoted as O_R, $mRNA$, E and T. The system can be described using a set of 8 reactions involving the production and loss (including degradation and dilution due to cell growth) of these four species. Description of the reactions and their reaction rates adapted from Bhartiya et al. (2006) are given in Table 1. For detailed description of the parameters, we refer to Bhartiya et al. (2006) and Santillan and Mackey (2001). The parameter values obtained from these references are summarised in Table 2.

Reactions	Description	Reaction rates
$O_t \to O_R$	Synthesis of free operators from total operators	$k_1 O_t \, K_{I1}^{n1} / (K_{I1}^{n1} + T^{n1})$
$O_R \to \varnothing$	Loss of free operon due to degradation and dilution	$(k_{d1} + \mu)O_R$
$O_R \to$ mRNA	Synthesis of mRNA through transcription	$k_2 O_R \, K_{I2}^{n2} / (K_{I2}^{n2} + T^{n2})$
mRNA $\to \varnothing$	Loss of transcripts due to degradation and dilution	$(k_{d2} + \mu)$ mRNA
mRNA $\to$ E	Synthesis of enzyme via translation	k_3 mRNA
E $\to \varnothing$	Loss of transcripts due to dilution	μ E
E $\to$ T	Synthesis of tryptophan catalysed by enzymes	$k_4 E \, K_{I3}^{n3} / (K_{I3}^{n3} + T^{n3})$
T $\to \varnothing$	Loss of tryptophan due to protein making and dilution	$(g/(T+K_g) + \mu)$ T

Table 1. System reactions and the associated rates.

Based on the reactions in Table 1, we set up below the SDEs of the Langevin model following the form of equations (5). The corresponding deterministic model of the Trp operon system can also be obtained from equations (6) by simply omitting the fluctuation terms or setting η=0 (Bhartiya et al., 2006).

$$\begin{aligned}
d(O_R) &= k_1 O_t \frac{K_{I1}^{n1}}{K_{I1}^{n1} + T^{n1}}dt - (k_{d1} + \mu)O_R dt + \\
&\quad \eta\sqrt{k_1 O_t \frac{K_{I1}^{n1}}{K_{I1}^{n1} + T^{n1}}}dW_1(t) - \eta\sqrt{(k_{d1} + \mu)O_R}\,dW_2(t) \\
d(mRNA) &= k_2 O_R \frac{K_{I2}^{n2}}{K_{I2}^{n2} + T^{n2}}dt - (k_{d2} + \mu)mRNA dt + \\
&\quad \eta\sqrt{k_2 O_R \frac{K_{I2}^{n2}}{K_{I2}^{n2} + T^{n2}}}dW_3(t) - \eta\sqrt{(k_{d2} + \mu)mRNA}\,dW_4(t) \\
d(E) &= k_3 mRNA dt - \mu E dt + \eta\sqrt{k_3 mRNA}\,dW_5(t) - \eta\sqrt{\mu E}\,dW_6(t) \\
d(T) &= k_4 E \frac{K_{I3}^{n3}}{K_{I3}^{n3} + T^{n3}}dt - \left(\frac{g}{T + K_g} + \mu\right)T dt + \\
&\quad \eta\sqrt{k_4 E \frac{K_{I3}^{n3}}{K_{I3}^{n3} + T^{n3}}}dW_7(t) - \eta\sqrt{\left(\frac{g}{T + K_g} + \mu\right)}dW_8(t)
\end{aligned} \quad (6)$$

To solve the SDEs above, the numerical algorithm we used is the Euler-Maruyama method (Gard, 1988). In all the simulations, a dt of 0.001 was used. We implemented the numerical algorithm for the SDEs using *Mathematica 5*. The addition of noise terms to the Langevin system of equations presented the problem that values could go negative. Because negative concentrations have no biological meaning, we needed to set boundary conditions to avoid them. In our simulation, we set any possible negative values to zero. Under most conditions, negative values were rare, however in certain conditions this can generate misleading result. By setting a lower boundary to the concentrations of all species, we guarantee non-negative values in the simulations.

Parameters	Value	Parameters	Value
k_1	50 min^{-1}	K_{I3}	810 μM
k_2	15 min^{-1}	n_1	1.92
k_3	90 min^{-1}	n_2	1.72
k_4	59 min^{-1}	n_3	1.2

k_{d1}	0.5 min^{-1}	u	0.01 min^{-1}
k_{d2}	15 min^{-1}	g	25 μM min^{-1}
K_{I1}	3.53 μM	K_g	0.2 μM
K_{I2}	0.04 μM	O_t	0.00332 μM

Table 2. Model parameter values

2.2. Derivation of the Gillespie Model

Another way to assess the effect of molecular noise is to describe the reaction steps as stochastic birth and death processes. Consequently, the stochastic dynamics of a biochemical system can be described by the means of the Chemical Master Equation and simulated using Gillespie algorithm (Gillespie, 1977).

A biochemical system is best implemented using Gillespie's algorithm when the detailed kinetic information of its individual elementary reactions are available. However, for many molecular systems, such complete set of kinetic rate constants of all reactions are not available. This is also the case for the tryptophan operon system. To accommodate this problem, we attribute to each linear and nonlinear term of the deterministic equations a probability of occurrence for the corresponding reaction (Gonze et al., 2002). Because the system reactions we set up before were simplified as unimolecular reactions, the propensity functions are therefore identical as the deterministic reaction rates(Gillespie, 1977). Transitions in terms of molecule numbers for each reaction channel are given in Table 3. Simulation of the Gillespie model was carried out using the improved Gibson-Bruck algorithm (Gibson & Bruck, 2000).

Reactions	Transitions
$O_t \rightarrow O_R$	$O_R \rightarrow O_R + 1$
$O_R \rightarrow \varnothing$	$O_R \rightarrow O_R - 1$
$O_R \rightarrow$ mRNA	mRNA$\rightarrow$ mRNA + 1
mRNA$\rightarrow \varnothing$	mRNA$\rightarrow$ mRNA - 1
mRNA$\rightarrow$ E	E $\rightarrow$ E + 1
E$\rightarrow \varnothing$	E $\rightarrow$ E + 1
E$\rightarrow$ T	T $\rightarrow$ T + 1
T$\rightarrow \varnothing$	T $\rightarrow$ T - 1

Table 3. Reaction transitions (the same notation was used here to denote molecule numbers).

3. EFFECT OF MOLECULAR NOISE ON THE TRYPTOPHAN OPERON SYSTEM

Before investigating the effect of molecular noise, we first examine the predictions produced from the deterministic model. For the parameter set in Table 2, typical dynamics of the tryptophan system predicted by the model shows that the concentration of the system species eventually settle to stable steady states after some transient period, regardless of the initial conditions which were used. Previous studies based on the deterministic model, however, did not investigate further the behaviour of the system beyond the given parameter values.

Motivated by recent suggestions that transcriptional bursting or the nature of birth and death of *mRNA* transcripts is a major source of noise at gene expression level (Kaern et al., 2005), we further explore the system behaviour by perturbating the mRNA degradation process. The rate at which mRNA degrades is controlled by parameter k_{d2}. We found that for the set of parameter given in Table 2, the deterministic tryptophan system exhibits sustained oscillatory behaviour at equilibrium when k_{d2} decreases below a threshold value of about 2.2. In the phase plane of enzyme versus tryptophan level, a limit cycle is approached as the system moves into equilibrium state. Shown in Figure 2 are the oscillatory patterns of the tryptophan level for three mRNA degradation rate: k_{d2} = 1, 1.2 and 1.5; together with their limit cycles in enzyme vs tryptophan phase plane. As k_{d2} moves further away from the bifurcation point towards oscillatory regime, the limit cycle size starts small and gets bigger indicating that this is a supercritical Hopf bifurcation.

Results from further bifurcation analysis shows that if level of total operon (O_t) is increased (O_t can be increased for example by means of constructing plasmids and inserting into the cell), the Hopf bifurcation point decreases. This means if the total of operon available is higher then periodic equilibrium is only possible at low degradation rates of *mRNA*.

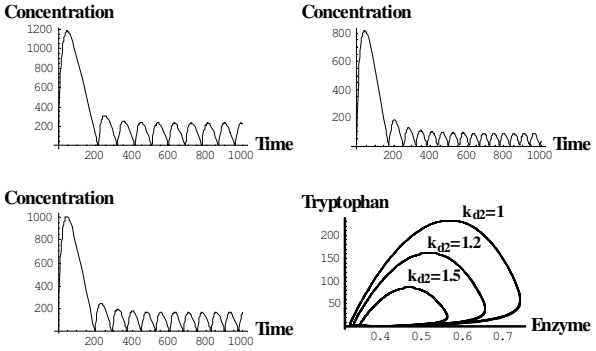

Figure 2. Sustained oscillations of tryptophan level predicted by the deterministic model; and limit cycles for k_{d2}=1, 1.2, 1.5

3.1. Effect Of Noise On Bifurcation Pattern

Turning into the effect of noise, we now consider the dynamical behaviour of the stochastic version based on the Langevin approach. As expected, with low noise coefficient (e.g. $\eta = 10^{-3}$), the stochastic predictions yield similar quantitative dynamics as in the deterministic regime except that in the stochastic model, small noisy fluctuations persist

around the deterministic concentrations. However, when noise level is large enough (e.g. $\eta = 5\text{x}10^{-3}$), stable sustained oscillations disappear for values of k_{d2} close to its bifurcation point. In fact, bifurcation analysis of the stochastic model identified a new bifurcation point for k_{d2} of around 1.5 (Figure 4), much lower compared to when noise is ignored. For k_{d2} below this new value, predicted system behaviour of stable oscillations is similar for both regimes. For comparison, we have produced as thick trajectories in Figure 3 the limit cycles (LCs) produced by the Langevin model, and thin trajectories the LCs produced by the deterministic model in enzyme versus tryptophan coordinates for two values of k_{d2} = 1.5 and 2. At k_{d2} = 1.5, the stochastic LC is noisy but stable, and having smaller average oscillation amplitude compared to the deterministic case. However, as k_{d2} is increased to 2, the stochastic LC has been reduced to a stable focus point with no exhibition of oscillations. On the other hand, we still observe a nice LC produced by the deterministic model.

Molecular fluctuations, when large enough, have been demonstrated to destroy oscillations in the tryptophan system in the vicinity of the bifurcation point. Furthermore, fluctuations have effectively replaced the bifurcation point from its deterministic position to a new, lower value. We show in Figure 4 the effects of internal noise on the bifurcation point for k_{d2}. Stochastic bifurcation diagram are plotted for 10 different realizations together with their mean.

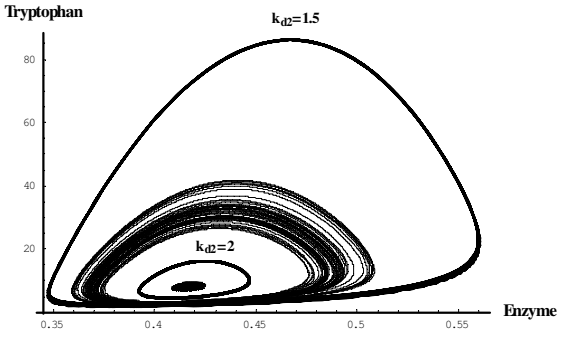

Figure 3. Stochastic and deterministic LCs for k_{d2} = 1.5 and 2 in the enzyme vs tryptophan concentration phase plane (see text for discussion).

3.2. Emergence of Stochastic Sustained Oscillations

In the previous section, we fixed other model parameters except for k_{d2} in order to investigate the influence of internal molecular noise on the system while changing the mRNA degradation rate.

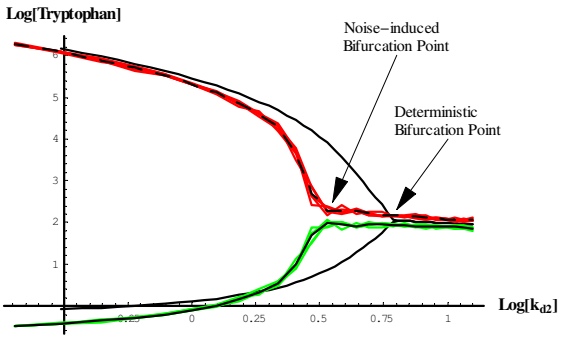

Figure 4. Deterministic compared to stochastic bifurcation diagrams (in log-scale) for parameter k_{d2} ($\eta = 0.005$).

In this section, we further investigate the difference in system dynamics emerged from comparing the stochastic and deterministic descriptions by varying the total operator concentration, O_t, while keeping other model parameters at values in Table 2. The deterministic model predicts stable steady state for the system over a wide range of tested values for O_t from 0 to 10 μM. On the other hand, when we apply molecular noise with sufficient level ($\eta = 10^{-2}$), the tryptophan system exhibits clear oscillatory dynamics with which we stochastically estimated a lower bifurcation point in [0.04,0.06] and a upper point in [0.8,1] (lower noise coefficient of $\eta = 10^{-3}$ did not show oscillations – Figure 5). These bifurcation points generally vary within the estimated ranges across different runs due to randomness. We plotted in Figure 5 the bifurcation diagram in log scale of the stochastic Langevin model in comparison with stable steady state of the deterministic model for two noise levels, $\eta = 10^{-3}$ and $\eta = 10^{-2}$.

Unlike the case in the previous section where internal noise has the effect of displacing the bifurcation point; noise has been seen here to induce stable sustained oscillations over parameter range with that, no such behaviour is predicted under the deterministic description. By stochastically modelling the tryptophan operon system, we have shown the emergence of qualitatively different dynamics when molecular noise is incorporated and pointed out marked differences in the predictions obtained from two modelling frameworks.

3.3. Prediction Of The Gillespie Approach

Besides the Langevin, we also carried out stochastic simulation using the Gillespie approach. Due to the high computational cost of the Gillespie's algorithm, we instead implemented the simulations with the Gibson-Bruck algorithm which manages to improve time performance substantially while

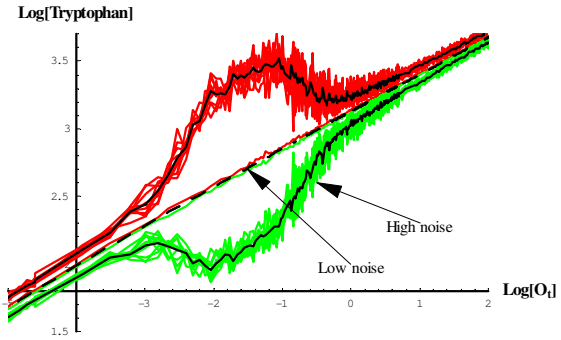

Figure 5. Stochastic bifurcation (in log-scale) for parameter O_t from 0.001 to 10 displayed with 10 realizations; the mean curves in solid black was calculated over 100 realizations ($\eta = 10^{-2}$). The dashed line represents the case when no noise is added.

maintaining the exactness of the algorithm (Gibson & Bruck, 2000).

For the parameter values and noise levels tested with the Langevin model, we obtained good agreement in predictions resulted from the two stochastic models (Figure 6). This shows that even without detailed kinetic knowledge of all elementary reactions involved in the system processes, our implementation of the Gillespie's method provides good predictions. The same approach could be used for systems in which only kinetic data on lumped reactions is available. Below we show the time evolution of tryptophan in concentration obtained from two stochastic model with same setting of noise level ($\eta = 10^{-3}$).

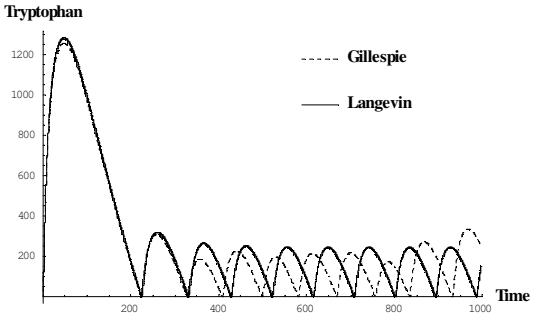

Figure 6. Time evolution of the tryptophan concentration predicted by the Gillespie approach in comparison with the Langevin equations approach

4. FLUCTUATION STRENGTH OF MOLECULAR COMPONENTS

One of the important topics in stochastic gene expression modelling is quantification of noise for different molecular components and processes within the genetic network. A quantitative picture of the network's internal fluctuations provides valuable knowledge into system behaviours under uncertain environments. Using the stochastic differential equations model, we aimed to quantify fluctuation strength for the molecular species in the tryptophan operon system. Normally, the fluctuation strength of a random variable μ is reported by its variance σ_μ^2. Thattai and Oudenaarden (2001) suggested to use the Fano factor (ratio of the variance to the mean) to measure the relative size of noise in gene expression. However, the Fano factor can be misleading for multivariate random processes and only works well for univariate discrete random processes (Paulsson, 2005). We adopted a preferred alternative measurement for noise which is formulated as the variance over the squared mean (Paulsson, 2005).

Simulation plots indicate that *mRNA* fluctuation level at steady state is much more significant that fluctuations of other molecular components. Quantitative results confirm that noise at *mRNA* is about from 3 to 5 orders of magnitude higher than that exhibited by enzyme and tryptophan level (Table 4). Noise is measured over 1000 simulation runs. Calculations are carried out using parameter values in Table 2; simulations start with zero level of all species. We also carried out the same measurement for various values of the *mRNA* degradation rate (k_{d2}) and found, as expected, that as k_{d2} is increased, *mRNA* fluctuation level is also increased. However, fluctuation level at all other component is decreased (Table 4). Therefore, to reduce noise output at the level of tryptophan, the degradation rate of transcripts should be increased.

k_{d2}	O_R	mRNA	Enzyme	Tryptophan
15	0.00066	0.12	4.78×10^{-6}	0.00065
30	0.00026	0.14	3.04×10^{-6}	0.00043
90	0.00005	0.35	2.36×10^{-6}	0.00022

Table 4. Noise strengths (noise coefficient $\eta = 10^{-2}$ was used).

5. DISCUSSION AND SUMMARY

The goal of this paper was to compare deterministic and stochastic models for a genetic regulatory network, thereby, studying the possible effects of molecular noise on system behaviour. In the presence of significant molecular noise, when the number of reacting molecules is small, stochastic modelling and simulations are necessary. We have constructed two stochastic models for the tryptophan operon system using two contemporary dominant frameworks: stochastic differential equations or the Langevin equations and the Gillespie's stochastic simulation. By means of such simulations, we have shown that noise at molecular level can result in oscillatory equilibrium for our tryptophan system. This behaviour is predicted only by means of stochastic modelling. The deterministic

model over the same parameter set could not predict oscillations but instead indicated that the system settles to a stable steady state. Furthermore, for cases when the deterministic model yields sustained oscillation at equilibrium, molecular noise has effectively displaced the bifurcation point by a significant distance. Nevertheless, the stochastic and deterministic bifurcation diagrams demonstrate similar patterns as the parameter moves away from the bifurcation point. For noise induced oscillations, we moreover found that the level of internal noise has quantitative effects on the amplitude and frequency of the oscillations. Higher noise levels within acceptable range result in limit cycle (in the enzyme versus tryptophan phase plane) with larger size and higher maximum value of tryptophan concentration. At very low level of noise, the stochastic model yields similar dynamics predicted by the deterministic counterpart. Discrepancies are more significant as the level of noise is increased.

As important as the qualitative information, quantitative information of noise also provides valuable insights into the nature as well as consequences of stochasticity within a particular biological system. We quantified noise strength for all key molecular species of the tryptophan system where fluctuation level is formulated as the variance divided by the squared mean. It is revealed that noise at *mRNA* is most significant while noise at enzyme is the smallest. This suggests that one possible strategy for reducing noise at the tryptophan level is to increase the degradation rate of *mRNA* transcripts.

To conclude, by explicitly including molecular noise in its formulation, stochastic modelling of the tryptophan operon system has provided more informative insights into the system behaviours compared to when only deterministic model is used.

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