Stochastic Process Algebra models of a Circadian Clock

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Abstract

We present stochastic process algebra models of a Circadian clock mechanism used in many biological organisms to regulate time-based behaviour. We compare modelling techniques from different modelling paradigms, PEPA and stochastic π-calculus.

1 Introduction

Many biological systems make use of a Circadian clock to keep track of the passage of time. The Circadian clock has evolved to create periodic concentrations of chemicals, in such a way that cells can regulate its behaviour according to the time of day or season of the year [1, 2].

With recent innovations in the use of stochastic process algebras to generate systems of ODEs or simulation models for huge state spaces, we will use the model of the Circadian clock to compare the biological modelling process in PEPA and stochastic π-calculus. This will be with a view to comparing simulation and numerical solution results of the same model in due course.

2 Circadian Clock

Figure 1 (taken from [1]) shows a biological graphical description of a Circadian clock with two DNA molecules for proteins A and R interacting through their respective mRNA molecules.

In the diagram, there are two DNA molecules, D_A and D_R, which describe proteins A and R. These DNA molecules generate mRNA molecules which in turn generate their respective proteins. High concentrations of the R protein absorb the A molecules and therefore R acts as a repressor for A. In the absence of A, R will degrade naturally. However, as A also acts as an activator for the generation of mRNA for both A and R molecules, we have several opportunities

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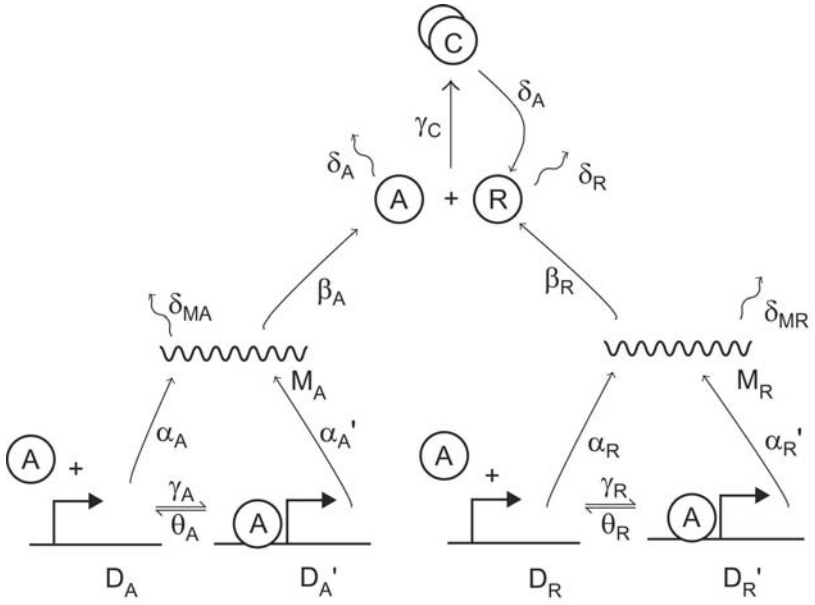

Fig. 1. The biological network for the Circadian clock.

for constructive and destructive feedback within the system. The result is that the concentration of A should oscillate in anti-phase to the concentration of R. The spikes in the concentration of A act as the ticks of a clock for an organism.

We use Figure 1 to create both stochastic π-calculus and PEPA models of the gene network.

3 Model

3.1 Modelling experience

3.1.1 Molecule creation

The major difference between modelling in stochastic π-calculus and PEPA is the way in which new molecules are generated. In stochastic π-calculus, it is succinct to have new molecules spontaneously appear in parallel out of individual molecule descriptions, as in:

$$D_A \stackrel{def}{=} \tau_{\alpha_A}.(D_A \mid M_A) \tag{1}$$

Here, after an exponential delay at rate α_A, a D_A molecule becomes a D_A and an M_A molecule. In effect, this means that the D_A molecule remains and an M_A molecule is spontaneously created.

In contrast, PEPA has a notion of a *bounded component structure* which encourages the creation of independent molecule lifecycles which capture an individual

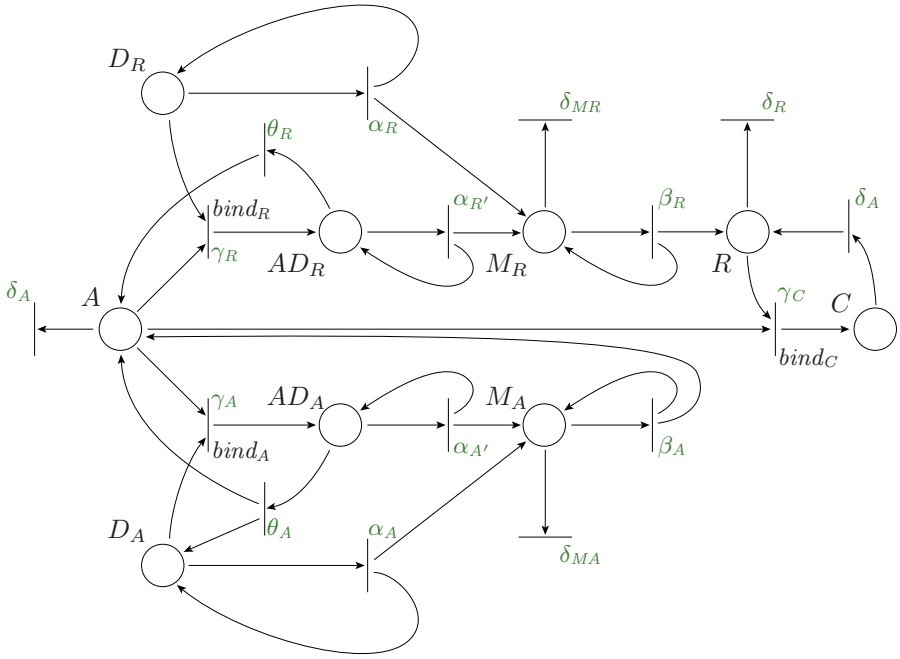

Fig. 2. An equivalent unbounded Petri net model of the gene/protein network

molecule's state, even if one of those states is just the potential to create the molecule. The PEPA equivalent of Equation (1) is given by:

$$\begin{aligned} D_A &\stackrel{def}{=} (trans_A, \alpha_A).D_A \\ M'_A &\stackrel{def}{=} (trans_A, \top).M_A \end{aligned} \tag{2}$$

Here the state M'_A represents the concept of there being sufficient resources in the system that, when driven by a $trans_A$ action from the DNA molecule D_A, an M_A molecule is instantiated.

3.1.2 Molecule creation: Ramifications

This single modelling difference between the formalisms has large implications.

1. To start with the stochastic π-calculus model can grow unboundedly, generating an indefinite number of M_A molecules. Whereas in the PEPA model, we would have to pre-specify the number of M_A molecules that the system was capable of creating using the following system equation:

$$D_A \underset{\{trans_A\}}{\bowtie} \underbrace{(M'_A \,||\, \cdots \,||\, M'_A)}_{n}$$

   Such a system would have the capacity to generate n molecules of M_A and no more.

As to which approach is appropriate, that will depend on the modelling situation and the facets of the system that the modeller is trying to capture.

2. The unbounded nature of the stochastic π-calculus model generates an infinite stochastic state space, which would make probabilistic model checking, in all but the most fortunate of cases, virtually impossible. So if tools such as PRISM, PEPA Workbench or ETMCC are to be employed to perform probabilistic analysis on biological systems, it would seem that the PEPA style of modelling has more potential.

   It should be noted though that if explicit state-space representation techniques are used by the tool, then even if a bounded and finite model is generated, only a very small version will be capable of being analysed as the state space quickly becomes unmanageable.

   The only practical way to analyse such large models is through continuous state-space representation via numerical ODE solution or stochastic simulation. As yet there is no model checking framework in which these techniques can be used.

3.1.3 Predefined synchronisation rate

Again comparing the same snippets of process model from Equation (1) and (2), we note that the rate of delay prior to molecule generation is defined as α_A. As discussed earlier this process is a succinct way of representing a synchronisation between the environment (the amino acids that are the building blocks of proteins and mRNA) and the DNA molecule. It could be said that as there was no explicit definition of how the individual processes participated in the synchronisation, that this does not produce a composable model. However, a counter argument would quite reasonably suggest that the action was τ-action anyway and not observable by other processes and that the above example was an abstraction of underlying cooperation.

3.2 Stochastic π-Calculus Model

$$
\begin{array}{rcl}
D_A & \stackrel{def}{=} & bind_{A_{\gamma_A}}.D_{A'} + \tau_{\alpha_A}.(D_A \mid M_A) \\
D_{A'} & \stackrel{def}{=} & \tau_{\theta_A}.(D_A \mid A) + \tau_{\alpha_{A'}}.(D_{A'} \mid M_A) \\
D_R & \stackrel{def}{=} & bind_{R_{\gamma_R}}.D_{R'} + \tau_{\alpha_R}.(D_R \mid M_R) \\
D_{R'} & \stackrel{def}{=} & \tau_{\theta_R}.(D_R \mid A) + \tau_{\alpha_{R'}}.(D_{R'} \mid M_R) \\
M_A & \stackrel{def}{=} & \tau_{\delta_{MA}}.\emptyset + \tau_{\beta_A}.(M_A \mid A) \\
M_R & \stackrel{def}{=} & \tau_{\delta_{MR}}.\emptyset + \tau_{\beta_R}.(M_R \mid R) \\
A & \stackrel{def}{=} & \overline{bind_{A_{\gamma_A}}}.\emptyset + \overline{bind_{R_{\gamma_R}}}.\emptyset + \overline{bind_{C_{\gamma_C}}}.\emptyset + \tau_{\delta_A}.\emptyset \\
R & \stackrel{def}{=} & bind_{C_{\gamma_C}}.C + \tau_{\delta_R}.\emptyset \\
C & \stackrel{def}{=} & \tau_{\delta_A}.R
\end{array}
$$

3.3 PEPA Model

$$
\begin{aligned}
D_A &\stackrel{def}{=} (bind_{AD_A}, \gamma_A).AD_A + (mk_{MA}, \alpha_A).D_A \\
AD_A &\stackrel{def}{=} (unbind_{AD_A}, \theta_A).D_A + (mk_{MA}, \alpha_{A'}).AD_A \\
D_R &\stackrel{def}{=} (bind_{AD_R}, \gamma_R).AD_R + (mk_{MR}, \alpha_R).D_R \\
AD_R &\stackrel{def}{=} (unbind_{AD_R}, \theta_R).D_R + (mk_{MR}, \alpha_{R'}).AD_R \\
M'_A &\stackrel{def}{=} (mk_{MA}, \top).M_A \\
M_A &\stackrel{def}{=} (decay_{M_A}, \delta_{MA}).M'_A + (mk_A, \beta_A).M_A \\
M'_R &\stackrel{def}{=} (mk_{MR}, \top).M_R \\
M_R &\stackrel{def}{=} (decay_{M_R}, \delta_{MR}).M'_R + (mk_R, \beta_R).M_R \\
A' &\stackrel{def}{=} (mk_A, \top).A \\
A &\stackrel{def}{=} (bind_{AD_A}, \gamma_A).A_{D_A} + (bind_{AD_R}, \gamma_R).A_{D_R} + (bind_{AR}, \top).A_C \\
&\quad + (decay_A, \delta_A).A' \\
A_{D_A} &\stackrel{def}{=} (unbind_{AD_A}, \top).A \\
A_{D_R} &\stackrel{def}{=} (unbind_{AD_R}, \top).A \\
A_C &\stackrel{def}{=} (unbind_{AR}, \top).A' \\
R' &\stackrel{def}{=} (mk_R, \top).R \\
R &\stackrel{def}{=} (bind_{AR}, \gamma_C).C + (decay_R, \delta_R).R' \\
C &\stackrel{def}{=} (unbind_{AR}, \delta_A).R
\end{aligned}
$$

The different process definitions represent the different states of the molecules in the system. The states M'_A, M'_R, A' and R' represent potential to create the molecules M_A, M_R, A and R. The system would start in the state with the potential to create n_X molecules of X for $X \in \{M_A, M_R, A, R\}$.

$$
\begin{aligned}
Circadian &\stackrel{def}{=} (D_A \parallel D_R) \underset{\mathcal{L}}{\bowtie} ((M'_A[n_{M_A}] \parallel M'_R[n_{M_R}]) \underset{\mathcal{M}}{\bowtie} (A'[n_A] \underset{\mathcal{N}}{\bowtie} R'[n_R])) \\
\mathcal{L} &= \{bind_{AD_A}, unbind_{AD_A}, bind_{AD_R}, unbind_{AD_R}, mk_{MA}, mk_{MR}\} \\
\mathcal{M} &= \{mk_A, mk_R\} \\
\mathcal{N} &= \{bind_{AR}, unbind_{AR}\}
\end{aligned}
$$

3.4 Parameters

The initial conditions and parameter values for the Circadian clock models are taken directly from [1]: $D_A = D_R = 1$ mol, $D'_A = D'_R = M_A = M_R = A = R = C = 0$, which require that the cell has a single copy of the activator and repressor genes: $D_A + D'_A = 1$ mol and $D_R + D'_R = 1$ mol.

$$
\begin{aligned}
\alpha_A &= 50h^{-1} & \delta_A &= 1h^{-1} \\
\alpha_{A'} &= 500h^{-1} & \delta_R &= 0.2h^{-1} \\
\alpha_R &= 0.01h^{-1} & \gamma_A &= 1mol^{-1}hr^{-1} \\
\alpha_{R'} &= 50h^{-1} & \gamma_R &= 1mol^{-1}hr^{-1} \\
\beta_A &= 50h^{-1} & \gamma_C &= 2mol^{-1}hr^{-1} \\
\beta_R &= 5h^{-1} & \theta_A &= 50h^{-1} \\
\delta_{MA} &= 10h^{-1} & \theta_R &= 100h^{-1} \\
\delta_{MR} &= 0.5h^{-1}
\end{aligned}
$$

4 Work in progress

We have generated and solved the ODE systems for both stochastic π-calculus and PEPA models and have reproduced the same results as obtained by Vilar *et al.* [1], in both cases. We note that restricting the capacity of the PEPA model to make key proteins upsets the phase of the Circadian rhythm, but does not destroy it altogether. We plan to explore this issue in a future publication.

We also intend to study further how the models differ from each other given the differing philosophies behind bounded (PEPA) and unbounded (stochastic π-calculus) modelling techniques. We would also like to see how the bounded capacity rate semantics of PEPA (use of the min function in synchronisation) compare to the mass action semantics of most biological and chemical modelling paradigms. We would like to know, in particular, what cooperation semantics in PEPA correspond to the mass action semantics in the final ODE/simulation model.

Acknowledgements

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References

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