Qualitative Reasoning of Stochastic Models and the Role of Flux

Paolo Ballarini[*], Maria Luisa Guerriero[†], and Jane Hillston[‡]

Abstract

Qualitative reasoning (QR) is a technique integrating the fields of AI and systems theory, whose aim is to be able to reason about the behaviour of systems with uncertainty in parameter values and in the exact quantitative dynamics. Traditionally applied to the study of the dynamics of physical systems, QR has been usually considered in a deterministic setting. Here we investigate the application of a QR approach to the analysis of continuous time Markov chains (CTMCs), and we focus on the application of probabilistic fluxes analysis as a first experiment in this context.

1 Introduction

Qualitative reasoning (QR) is an approach to analysing dynamic systems at a level of abstraction which disregards precise quantitative parameters but nevertheless is able to derive information about the possible behaviours which might be exhibited by the system [6, 7]. It has been primarily studied in AI and can be regarded as a form of knowledge representation. It is sometimes likened to *common-sense* reasoning, the analogy being that we can all predict the behaviour of many physical dynamic systems, such as the swinging of a pendulum, without having to analyse the differential equation which precisely governs that behaviour. Motivations for QR include uncertainty about parameter values, uncertainty about the initial conditions of the system, or even explicit uncertainties in the model, for example with stochastic differential equations [4]. Applications of QR include diagnostics, fault prediction, planning, argumentation and explanation.

Recently QR has been proposed in the context of systems biology [1, 5]. In biochemical systems biologists often characterise behaviour based on the qualitative trends of proteins concentrations rather than quantitative amounts. There are several reasons for this:

- parameter values for models of biochemical systems are rarely known in detail;
- the models themselves may be based on partial knowledge and speculation;
- difficulties in exactly repeating the same experiment, and the indirect forms of measurement used, make it difficult to characterise a behaviour quantitatively.

Given its origins in modelling physical systems QR is usually applied to systems of differential equations which have deterministic behaviour. The motivation for this paper is to consider whether there is scope to develop an approach to QR for stochastic models of dynamic behaviour.

[*]CoSBi, Trento, Italy. Email: ballarini@cosbi.eu
[†]University of Edinburgh, Scotland, UK. Email: mguerrie@inf.ed.ac.uk
[‡]University of Edinburgh, Scotland, UK. Email: jane.hillston@ed.ac.uk

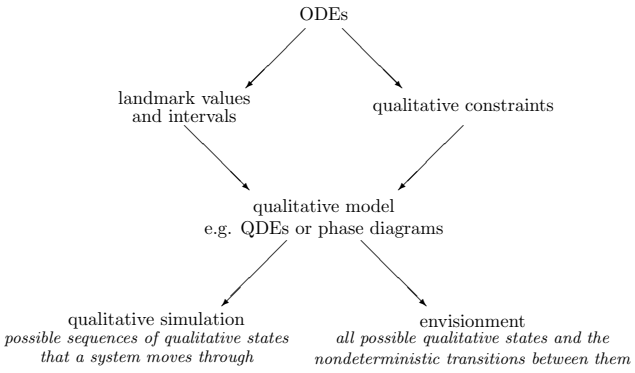


Figure 1: Schematic view of QR reasoning.

This is preliminary work and the current paper is intended to explore the issues which may be involved rather than present any definitive answers.

2 Qualitative Reasoning

A number of different styles of qualitative modelling have appeared in the literature but they all start from a continuous, generally deterministic, representation of the dynamics of a system, usually as a set of ordinary differential equations (ODEs). Abstraction is applied to the system so that rather than look at the continuum of possible values for variables within the equations, instead a discrete set of intervals is identified. The boundaries between intervals are important and termed *landmark* values for the variables. In the simplest case the landmark values might be just $-\top, 0, \top$, creating the intervals $(-\top, 0)$ and $(0, \top)$ i.e. we only distinguish whether a value is negative or positive. If the differential equation governing the behaviour of the variable includes higher derivatives (i.e. the differential equation is higher than first order) each derivative is treated as a distinct variable. Thus if we consider a ball thrown vertically into the air, its height at time t is given by

$$x(t) = -\frac{1}{2}gt^2 + v_0t + x_0$$

and the variables correspond to the height and the velocity. The height may be positive or 0, whereas the velocity may be positive, negative or zero.

Which ever style of qualitative modelling is used, the steps of QR are broadly the same and as illustrated in Figure 1. The potential qualitative states can be found by considering the product space derived from the qualitative states of each variable. However, in general it will not be possible to reach all these states as the dynamics of the system places constraints on its behaviour. For example, once the velocity of the ball has reached zero it is no longer possible for the height of the ball to increase. Applying the qualitative constraints to the product state space reduces it to the qualitative model which may be represented as a phase diagram or a set of qualitative differential equations for example. In essence this captures which combinations of intervals and values for variables are valid. This representation may then be subjected to *simulation* to derive valid trajectories, or *envisionment*. An envisionment is the state transition diagram for the qualitative state space. It may be either a *total* envisionment, considering all valid states, or an *attainable* envisionment, showing only those states reachable from known

initial conditions.

In some systems we may gain more understanding of the behaviour of the system if as well as the qualitative value of state variables we also have qualitative information about its derivative. For example, if we consider a swinging pendulum, knowing that the velocity is positive does not characterise the different behaviours in different parts of the trajectory. However if we also know how the rate of change of velocity is varying we gain a more complete view of the behaviour. Thus some QR systems incorporate not just variable intervals and landmarks into their representation of qualitative states, but also derivative intervals and landmarks [2].

There has been some work interpreting the envisionment as the state transition diagram for a Markov process and then subjecting it to usual Markov analysis [4]. In this case probabilities must be attributed to each of the transitions within the state space. In [4] this is done using a relative frequency argument. Doyle and Sacks work with a phase transition QR model and choose the probabilities according to the proportion of points within the volume of phase space corresponding to the abstract state which will follow a trajectory leading to another abstract state within one time unit. Once the Markov chain is generated they propose analysing it to identify transient and ergodic states, as well as usual Markovian analysis to find steady state and time to absorption in the case of an absorbing Markov chain. Note that this is quite different from what we are interested in. Here the stochasticity is added only after the derivation of the qualitative state space as a means to assess which (deterministic) behaviour is more likely. We are interested in replacing the dynamic model on which the QR is based by a continuous time Markov chain (CTMC).

3 Flux-based Analysis: a First Experiment on Stochastic Qualitative Reasoning

We will consider CTMC models which might arise from consideration of systems composed of interacting components, for example PEPA models. Thus the dimensions of our CTMC will correspond to the possible local states of the components, and our state representation will be the count of the number of components exhibiting each local state. These will be variables which QR would seek to abstract. Therefore note that the high/low style of PEPA modelling, and Bio-PEPA with levels, could already be viewed as qualitative representations of the system, with the PEPA/Bio-PEPA semantics providing the qualitative constraints, and the derived state space being an attainable envisionment.

However this is not the focus of our current experiment. Here we aim to investigate alternative, possibly more abstract, ways of viewing the dynamics of a CTMC. In general, the quantitative dynamics of CTMC are studied in two ways.

- By simulation, in which one possible trajectory through the state space is generated at a time, exhibiting one possible result of the stochastic choices within the system. Multiple trajectories must be generated before any conclusions can be drawn about the behaviour of the system. However the behaviour which is observed is definitive in the sense that there is a clear progression from state to state.
- By numerical solution of the state probability distribution, considering all possible behaviours at the same time. Here what is observed is not a progression from state to state but a shifting of probability mass within the probability distribution as some states become more likely than others over time.

It is not straightforward to map either of these directly to the ODE characterisation of system dynamics on which QR is usually based. Like simulation the ODE could be regarded as a linear

time view, as a single trajectory is observed. However, in many ways this trajectory is related to the expected value of state variables which might be observed in numerical solution of the CTMC as the ODE dynamics allows all possible actions to occur at once. In other words the ODE trajectory corresponds to the expected value of the state variables in the CTMC. Thus we have chosen this latter view of the CTMC and wish to consider how analysis of the probability distribution and the forces governing its evolution may be used for QR.

CTMC models are characterised by a *steady-state* and a *transient window*. Starting at time $t = 0$ the model eventually reaches its steady-state within a given time $t_{ss} > 0$. The time interval $[0, t_{ss}]$ is the *transient window* of the CTMC model. However note that this notion of steady-state is quite different to that considered in the QR literature, where due to the deterministic nature of the dynamic model the steady-state is a single, absorbing state.

In the rest of this section we focus on *probabilistic fluxes* into/out of a given state of a (finite state) CTMC model, and we investigate their use for the analysis of the (qualitative) dynamic behaviour of the CMTC. First we give a few relevant definitions, and then we show the result of flux-based analysis on a few simple systems.

An $(n \geq 1)$-dimensional CTMC M is characterised by a set of n non-negative integer valued variables $(X^1, X^2, \cdots, X^n)$, and a state $s_j = (x_j^1, x_j^2, \cdots, x_j^n) \in S$ is an n-tuple representing the values of each variable X^i in state s_j.

A transition $q : s_j \to s_k$ (with $s_j = (x_j^1, x_j^2, \cdots, x_j^n)$ and $s_k = (x_k^1, x_k^2, \cdots, x_k^n)$) such that $Q(s_j, s_k) > 0$ is called an X^i-*increasing* transition if and only if $(x_j^i < x_k^i)$. Similarly, q is called X^i-*decreasing* iff $(x_j^i > x_k^i)$, and X^i-*invariant* iff $(x_j^i = x_k^i)$.

Given an n-dimensional CTMC $M = (S, Q, s_0)$, a state $s_j = (x_j^1, x_j^2, \cdots, x_j^n) \in S$, and a variable X^i (with $1 \leq i \leq n$), we define $E_{+i}(s_j), E_{-i}(s_j), E_{=i}(s_j) \leq E(s_j)$ as the outgoing rates from state s_j corresponding to, respectively, X^i-increasing, X^i-decreasing and X^i-invariant transitions (and we call them X^i-increasing, X^i-decreasing, and X^i-invariant outgoing rates). Formally, they are defined in Eq. (1), Eq. (2) and Eq. (3), respectively.

$$E_{+i}(s_j) = \begin{cases} \sum_{1 \leq k \leq m, k \neq j} Q(s_j, s_k) & \textbf{if } \; x_j^i < x_k^i \\ 0 & \textbf{otherwise} \end{cases} \tag{1}$$

$$E_{-i}(s_j) = \begin{cases} \sum_{1 \leq k \leq m, k \neq j} Q(s_j, s_k) & \textbf{if } \; x_j^i > x_k^i \\ 0 & \textbf{otherwise} \end{cases} \tag{2}$$

$$E_{=i}(s_j) = \begin{cases} \sum_{1 \leq k \leq m, k \neq j} Q(s_j, s_k) & \textbf{if } \; x_j^i = x_k^i \\ 0 & \textbf{otherwise} \end{cases} \tag{3}$$

These tell us the rates of change to particular variables in particular states but since we view the system through its probability distribution we need to instead consider the expected values for these rates of change, i.e. the probabilistic flux. Given a state $s \in S$, and a time instant $t \in \mathbb{R}_+$, we define the *instantaneous state out-flux* as follows.

Definition 1 (Instantaneous state out-flux) *The* instantaneous state out-flux *for s at time t is defined as:*

$$flux(s, t) = \pi(s, t) \cdot E(s) = \pi(s, t) \cdot -Q(s, s) \ .$$

The out-flux for state s at time t is computed as the product of the transient probability of being in state s at time t (i.e. $\pi(s, t)$) multiplied by the emanating rate from s (i.e. the sum of rates of all its outgoing transitions).

We can now define the i^{th}-*dimensional instantaneous state out-flux* and the i^{th}-*dimensional instantaneous total out-flux.*

Definition 2 (Instantaneous i^{th}-dimensional state out-flux) *The* instantaneous i^{th}-dimensional increasing/descreasing/invariant state out-fluxes *for s at time t (with $1 \leq i \leq n$) are defined as:*

$$flux_{+_i}(s,t) = \pi(s,t) \cdot E_{+i}(s)$$
$$flux_{-_i}(s,t) = \pi(s,t) \cdot E_{-i}(s)$$
$$flux_{=_i}(s,t) = \pi(s,t) \cdot E_{=i}(s)$$

where $E_{+i}(s), E_{-i}(s), E_{=i}(s) \leq E(s)$ are the X^i-increasing, X^i-decreasing, and X^i-invariant outgoing rates from s.

The i^{th}-dimensional increasing/decreasing/invariant state out-flux are, hence, the portions of $flux(s,t)$ corresponding to, respectively, X^i-*increasing*, X^i-*decreasing* and X^i-*invariant* transitions.

The X^i-*instantaneous gradient state out-flux*, denoted as $flux_{\delta i}(s,t)$ is defined as the difference between the increasing and the decreasing fluxes:

$$flux_{\delta i}(s,t) = flux_{+_i}(s,t) - flux_{-_i}(s,t) \ .$$

Definition 3 (Instantaneous i^{th}-dimensional total out-flux) *The* instantaneous i^{th}-dimensional increasing/descreasing/invariant/gradient total out-fluxes *at time t (with $1 \leq i \leq n$) are defined as:*

$$flux_{+i}(t) = \sum_{s \in S} flux_{+i}(s,t)$$
$$flux_{-i}(t) = \sum_{s \in S} flux_{-i}(s,t)$$
$$flux_{=i}(t) = \sum_{s \in S} flux_{=i}(s,t)$$
$$flux_{\delta i}(t) = \sum_{s \in S} flux_{\delta i}(s,t)$$

The total i^{th}-dimensional out-fluxes (increasing/decreasing/invariant/gradient) for the CTMC M at time t are the sum, over all states of M, of the i^{th}-dimensional increasing/decreasing and invariant/gradient fluxes at time t (again, for the sake of readability, M is omitted from the notation of total fluxes).

Definition 4 (i^{th}-dimensional flux analysis of CTMC) *Let $T = [t_1, t_2]$ be a time interval (with $t_1 < t_2 \in \mathbb{R}^+$), $F \in \mathbb{N}^*$ be the sampling frequency of T, and $\Delta = \| \frac{(t_2 - t_1)}{F} \|$ be the sampling period denoting the amplitude of each sub-interval of T. The* i^{th}***-dimensional flux analysis*** *for a given CTMC M over the time interval T is achieved through calculation of the increasing/decreasing/invariant/gradient fluxes for M over the time interval T and with respect to the sampling period Δ.*

In the next section we show some results of the flux-analysis for a few simple models.

3.1 Flux analysis of CTMC: Some Examples

We consider few examples of multi-dimensional CTMCs modelling elementary biochemical systems. The number of dimensions of each such a CTMC corresponds to the number of biochemical species in the considered system. In each one of the following examples we calculate the positive, the negative, the invariant as well as the gradient flux of each dimension (i.e. species). We discuss the obtained results by comparing the flux behaviour with classical transient analysis.

3.1.1 $A \to B \to C$

We consider the 3-dimensional CTMC model corresponding to the biochemical system described by reactions:

$$\begin{aligned} A &\to B \\ B &\to C \end{aligned} \tag{4}$$

Equations (4) are an example of simple *closed system* (i.e. the total population is invariant) representing the transformation of molecules of a source species A into molecules of a target species C via an intermediate species B. For simplicity we assume the two reactions to be *balanced* (i.e. having the same rate) and we consider an initial configuration with only 10 molecules of A (i.e. we assume $(10, 0, 0)$ to be the initial state). We observe that the corresponding CMTC has $(n+1)(n+2)/2$ states (where $n = a_0$ is the initial amount of A) with exactly one deadlock state (i.e. $(0, 0, n)$). The dynamics of such a system is intuitively pretty simple: starting at time $t = 0$ species A will monotonically decrease to 0, while its dual, species C, will monotonically increase to $n = 10$. On the other hand the intermediate species B will have a peak corresponding to the progressive *transformation* of A into C. The *transient* behaviour of species A, B and C is depicted in Figure 2, where each line represents the *instant reward* of a version of the CTMC model with state rewards (i.e. rewards corresponding to the level of each species have been assigned to each state of the chain): this corresponds to the expected value of the species at that time. Figure 2 reflects the intuition with A and C monotonically increasing and decreasing, respectively, throughout the transient window, and with B peaking after about 1 time unit.

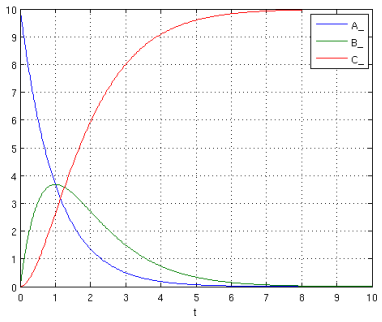
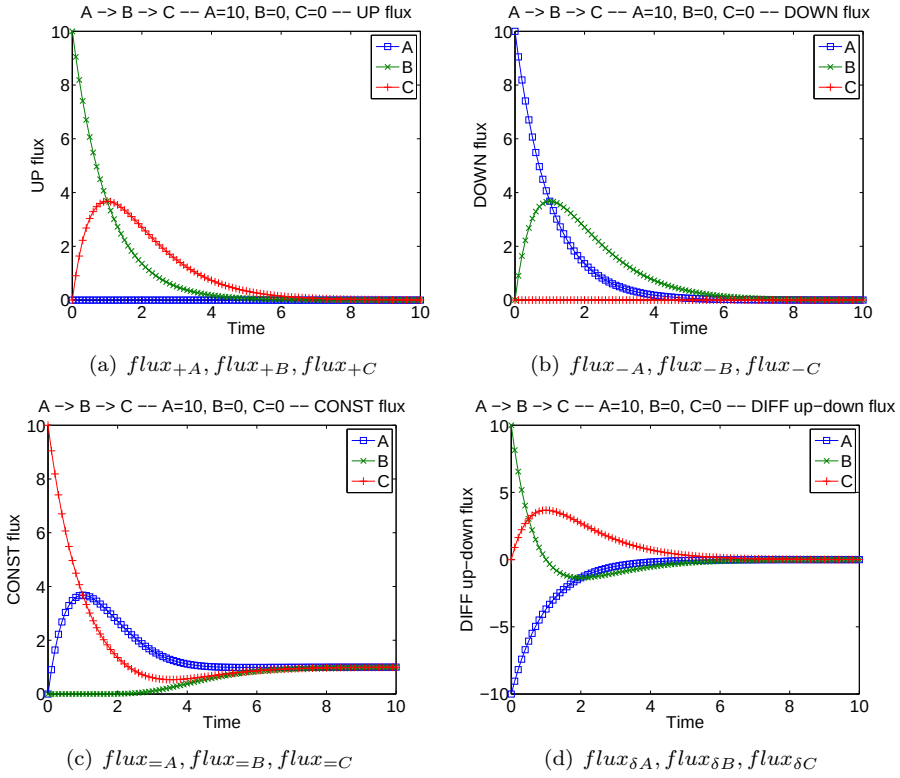


Figure 2: Instant reward (transient analysis) of the $A \to B \to C$ model.

The interpretation of fluxes is also in compliance with the intuitive description of the system behaviour, however it requires a little bit more thinking. With respect to the positive fluxes (Figure 3(a)) we observe that A-positive flux (blue line) is constantly null, as A cannot increase at all in this system. On the other hand, B-positive flux (green line), starting from its maximum level (corresponding to the maximal rate of conversion of A into B), steadily decreases up until

all A molecules have turned into B molecules. Finally the C-positive flux for (red line) shows a peak representing the maximal speed at which C is produced and which happens slightly after B has reached its peak (i.e. at $t = 1$, compare the green line of Figure 2 with the red line of Figure 3(a)), which is: when half of the A molecules has turned into B molecules. The interpretation of the negative fluxes (Figure 3(b)) and invariant fluxes (Figure 3(c)) can be devised similarly. Finally we spend a few words commenting on the gradient fluxes (Figure 3(d)) because they provide the most significant source of *qualitative* information about the dynamics of a CTMC model. Figure 3(d) illustrates the *qualitative* behaviour of the system within the transient window. Specifically we observe that A-gradient flux (blue line) is always negative, signifying that the overall amount of A will constantly decrease. On the other hand, C-gradient flux (red line) is always positive, meaning that the overall amount of C will only increase in the system, although the presence of a peak tells us that the speed of such growth will progressively slow down after an initial *acceleration*. Finally, B-gradient flux (green line) spans from (strongly) positive to (weakly) negative, meaning that after an initial fast growth, the increase in B will slow down and eventually turn into a decrease.



(a) $flux_{+A}, flux_{+B}, flux_{+C}$ (b) $flux_{-A}, flux_{-B}, flux_{-C}$

(c) $flux_{=A}, flux_{=B}, flux_{=C}$ (d) $flux_{\delta A}, flux_{\delta B}, flux_{\delta C}$

Figure 3: Fluxes calculation for the $A \to B \to C$ model.

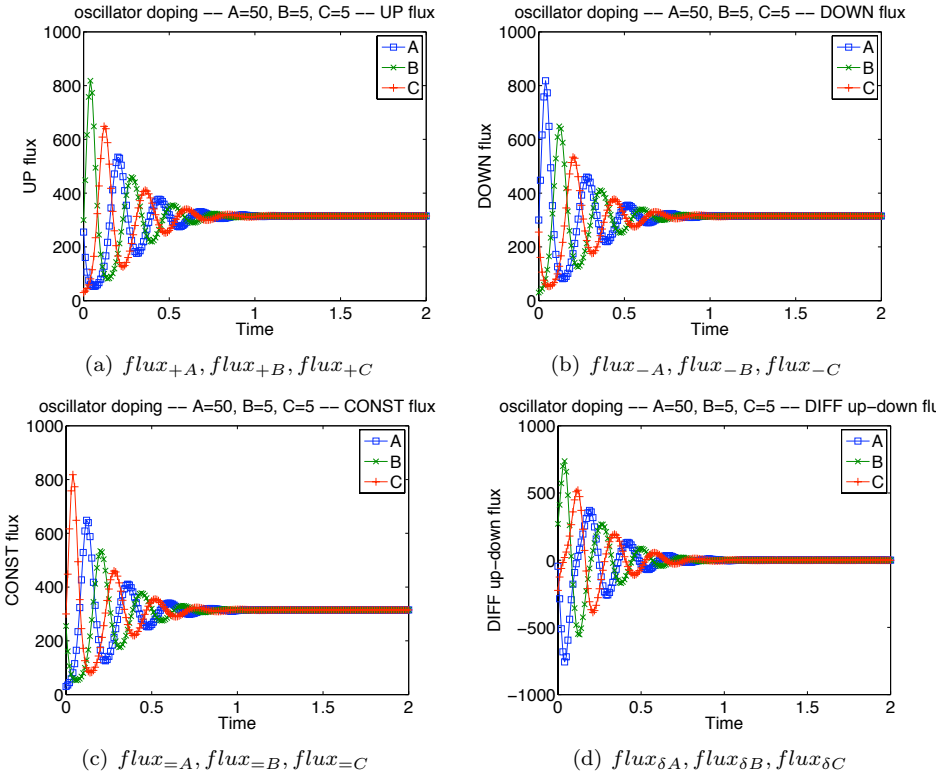
3.1.2 A 3-way oscillator.

As a further example of CTMC flux analysis we consider a slightly more complicated system, known as the 3-way oscillator [3]. The model is (as in the previous case) a 3-dimensional CTMC

model corresponding to the biochemical system described by the following 3 + 3 reactions[1]:

basic reactions	**doping reactions**
$A + B \rightarrow B + B$	$D_A + B \rightarrow A + D_A$
$B + C \rightarrow C + C$	$D_B + C \rightarrow B + D_B$
$C + A \rightarrow A + A$	$D_C + A \rightarrow C + D_C$

Species D_A, D_B and D_C represent *doping substances* for the main species, respectively A, B and C. Stochastic simulations show a permanent oscillation for the above system: the levels of molecules for the three species A, B and C fluctuate permanently and in a co-ordinated fashion. The presence of the *doping reactions* guarantees that the oscillation does never stop. In this case the resulting CTMC model is finite-state and ergodic (no deadlock states). We also consider the *no-doping* variant of such model, whereby doping reactions (and species) are removed. In this case the system still oscillates; however, the oscillation damps down in finite time (i.e. the underlying CTMC has 3 deadlock states corresponding to all molecules accumulating in either A, B or C).



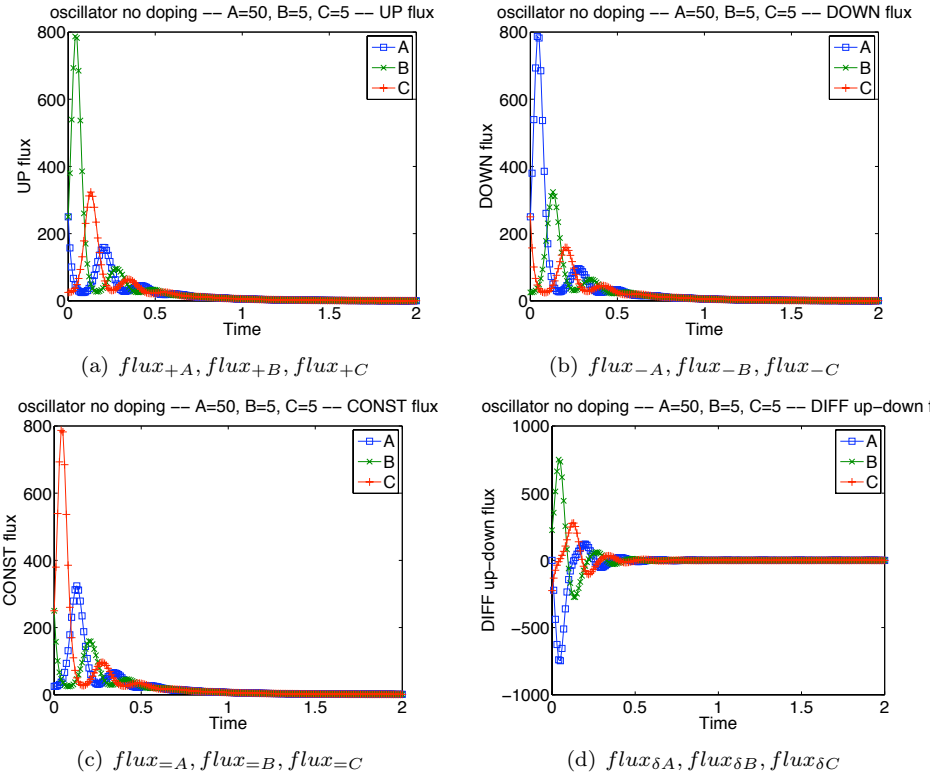
(a) $flux_{+A}, flux_{+B}, flux_{+C}$ (b) $flux_{-A}, flux_{-B}, flux_{-C}$

(c) $flux_{=A}, flux_{=B}, flux_{=C}$ (d) $flux_{\delta A}, flux_{\delta B}, flux_{\delta C}$

Figure 4: Fluxes calculation for the 3-way oscillator model with doping.

[1]Note that even though there are actually 6 species in this systems, the underlying CTMC is still 3-dimensional, as three of the species, namely D_A, D_B and D_C, are just *modifiers* (i.e. neither *reactants* nor *products*), and thus their amounts do not need to be captured in the state.

Results of flux calculations for a version of the model with initial state $(50, 5, 5)$ are showed in Figure 4 for the oscillator with doping (i.e. sustained oscillation) and in Figure 5 for the oscillator without doping reactions (i.e. damped oscillation).



(a) $flux_{+A}, flux_{+B}, flux_{+C}$

(b) $flux_{-A}, flux_{-B}, flux_{-C}$

(c) $flux_{=A}, flux_{=B}, flux_{=C}$

(d) $flux_{\delta A}, flux_{\delta B}, flux_{\delta C}$

Figure 5: Fluxes calculation for the 3-way oscillator model without doping.

In both cases the oscillatory behaviour of the system is reflected by the fluxes, although the sustainability of the doped oscillator clearly cannot be observed through fluxes because of their *transient nature*: the oscillatory trend of the fluxes fades away as the steady state is approached.

The main difference between the doped and non-doped oscillators is reflected by the fact that at steady-state fluxes stabilise at a positive value for the sustained oscillator, and at zero for the damped oscillator. Furthermore, if we compare, for example, the positive fluxes of the sustained (Figure 4(a)) and damped (Figure 5(a)) oscillators, we observe that C-positive flux grows much faster in the doped oscillator than in the non-doped one. This is due to the presence of the doping reactions (and, specifically, of reaction $D_C + A \rightarrow C + D_C$) which boost the production of C molecules proportionally to the amount of A (which in the initial state $(50, 5, 5)$ is indeed large); in the non-doped case, instead, the growth of C is due, exclusively, to transformation of B into C (i.e. reaction $B + C \rightarrow C + C$) which, due to the low (initial) level of B, makes the growth of C much slower.

4 Conclusion

In this paper we have explored the information which can be gained from considering the probabilistic flux acting on state variables in a CTMC. We have demonstrated that this provides an interesting alternative view of the dynamics of the system. However this cannot currently be regarded as qualitative reasoning as both states and rates are represented in full and not abstracted. Moreover, the approach we take, by sampling the probabilistic flux using transient analysis of the CTMC, is computationally intensive and would not be feasible for large systems. Nevertheless this appears to be a rich topic for further exploration.

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