

# *Modelling Biochemical Reaction Networks*

## *Lecture 16:*

### *Gene expression and delay-differential equations*

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## *Back to chemical kinetic theory*

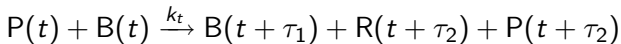
- ▶ When we say that  $A + B \rightarrow C$  is an elementary reaction, we mean that, after some collisions of an A and a B, a transition state is formed which rapidly leads to the product C.
- ▶ The rate constant is determined by two factors:
  - ▶ how often collisions between A and B occur, and
  - ▶ how likely A and B are to react once they have collided.

## *Delayed effects*

- ▶ Transcription and translation are not elementary processes.
- ▶ However, taking transcription as an example, we can talk about how often transcription factors bind and how likely they are to initiate transcription.
- ▶ There is an additional factor to take into account, namely how likely transcription is to complete.
- ▶ By analogy to conventional chemical kinetic theory, these factors can be represented by a rate constant.
- ▶ However, the product (RNA) only appears after a significant delay.
  - ▶ Typical transcription/translation times in bacteria: 1–2 min
  - ▶ Typical transcription times in yeast: 1–3 min
  - ▶ Typical transcription times in multicellular eukaryotes: 5–40 min
  - ▶ Typical translation times in eukaryotes: 2–4 min

## *Processes with delayed effects*

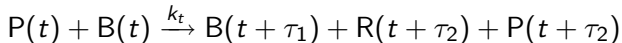
- ▶ As an example, consider transcription of DNA to RNA (R) by RNA polymerase (P). The polymerase binds to a promoter (binding) site (B) on the DNA where transcription initiation occurs.
- ▶ We can model transcription by a reaction with a delayed effect:



How to read this reaction: if P binds B at time  $t$ , the promoter is cleared (available for a new round of transcription)  $\tau_1$  time units later, and transcription completes, liberating RNA and the polymerase,  $\tau_2$  time units after initiation.

# *Processes with delayed effects*

## *Rate equations*



- ▶ If we want to model this process in a single cell, we should use a stochastic model.
- ▶ Assume instead that we are interested in the average behavior over a large number of cells so that we can use rate equations.

## *Processes with delayed effects*

*Rate equations*

$$P(t) + B(t) \xrightarrow{k_t} B(t + \tau_1) + R(t + \tau_2) + P(t + \tau_2)$$

- ▶ The rate equations obey the law of mass action except that initiation and product formation are separated in time. In other words, the rate of product formation depends on the rate of initiation at an earlier time:

$$\begin{aligned}\frac{dP(t)}{dt} &= -k_t P(t)B(t) + k_t P(t - \tau_2)B(t - \tau_2) \\ \frac{dB(t)}{dt} &= -k_t P(t)B(t) + k_t P(t - \tau_1)B(t - \tau_1) \\ \frac{dR(t)}{dt} &= k_t P(t - \tau_2)B(t - \tau_2)\end{aligned}$$

## *Delay-differential equations*

$$\begin{aligned}\frac{dP}{dt} &= -k_t P(t)B(t) + k_t P(t - \tau_2)B(t - \tau_2) \\ \frac{dB}{dt} &= -k_t P(t)B(t) + k_t P(t - \tau_1)B(t - \tau_1) \\ \frac{dR}{dt} &= k_t P(t - \tau_2)B(t - \tau_2)\end{aligned}$$

- ▶ These equations are a set of **delay-differential equations** (DDEs).
- ▶ The solutions depend on the history, i.e. on prior values of the solution.

## *Delay-differential equations*

*Initial function*

$$\begin{aligned}\frac{dP}{dt} &= -k_t P(t)B(t) + k_t P(t - \tau_2)B(t - \tau_2) \\ \frac{dB}{dt} &= -k_t P(t)B(t) + k_t P(t - \tau_1)B(t - \tau_1) \\ \frac{dR}{dt} &= k_t P(t - \tau_2)B(t - \tau_2)\end{aligned}$$

- ▶ The initial condition for a set of DDEs is an **initial function**: necessary in order for the right-hand sides to be defined at the beginning of the integration.
  - ▶ In this case, we need a vector-valued function  $\mathbf{f}(t)$  such that

$$(P(t), B(t)) = \mathbf{f}(t) \quad \text{for } -\tau_2 \leq t \leq 0$$

given that, physically,  $\tau_2 > \tau_1$ .



## *Delay-differential equations*

### *Initial function*

- ▶ The initial function is arbitrary, although in some cases, it can be chosen to reflect a particular type of experiment.

**Example:** If the promoter (B) is occluded by a transcription inhibitor until  $t = 0$ , a suitable initial function might be

$$P(t) = P_0 \quad \text{for } -\tau_2 \leq t \leq 0$$
$$B(t) = \begin{cases} 0 & \text{for } -\tau_2 \leq t < 0 \\ B_0 & \text{for } t = 0 \end{cases}$$

## *Delay-differential equations*

### *Knots*

- ▶ In our example, from  $-\tau_2$  to 0, the values of  $P$  and  $B$  are given by the initial function.
- ▶ From 0 to  $\tau_2$ , the values of  $P$  and  $B$  are computed from the DDEs, with the history-dependent terms computed from the initial function.  
 $\implies$  1st derivative discontinuous at  $t = 0$ .
- ▶ From  $\tau_2$  to  $2\tau_2$ ,  $P$  and  $B$  are computed from the DDEs, with the history-dependent terms computed from the solution on  $t \in (0, \tau_2]$ .  
The DDEs govern the dynamics over the entire range  $t \in (0, 2\tau_2]$ , but since the first derivative was discontinuous at  $t = 0$ , integrating through  $t = \tau_2$  introduces a discontinuity in the second derivative of the solution at this  $t$ .
- ▶ In general, the  $n$ 'th derivative is discontinuous at the **knot**  $t = (n - 1)\tau_2$ .

## *Delay-differential equations*

### *Mass conservation in DDEs*

- ▶ We can think of a delayed term as a pipe: Material goes in one end, and takes some time to come out the other end.
- ▶ The total amount of material in the system at any time therefore includes material in the pipe.
- ▶ The total amount of material can be calculated by imagining that we can stop all reaction initiations, i.e. dropping all the corresponding terms in the DDEs.  
The remaining (delayed) terms correspond to “flushing out the pipe”.
- ▶ The most convenient time to carry out this operation is at  $t = 0$  since the concentrations are given by the initial function before this time.

## *Delay-differential equations*

### *Mass conservation in DDEs*

- ▶ In our model, crossing out the initiation terms gives

$$\begin{aligned}\frac{dP}{dt} &= -\cancel{k_t P(t) B(t)} + k_t P(t - \tau_2) B(t - \tau_2) \\ \frac{dB}{dt} &= -\cancel{k_t P(t) B(t)} + k_t P(t - \tau_1) B(t - \tau_1)\end{aligned}$$

- ▶ Rearrange and integrate:

$$\begin{aligned}dP &= k_t P(t - \tau_2) B(t - \tau_2) dt \\ \therefore P(t) - P(0) &= \int_0^t k_t P(\xi - \tau_2) B(\xi - \tau_2) d\xi \\ \text{or } P(t) &= P(0) + \int_0^t k_t P(\xi - \tau_2) B(\xi - \tau_2) d\xi\end{aligned}$$

## *Delay-differential equations*

### *Mass conservation in DDEs*

- ▶ Since reaction initiations are assumed to have stopped at  $t = 0$ ,

$$\begin{aligned}P_{\text{total}} &= P(0) + \int_0^{\tau_2} k_t P(\xi - \tau_2) B(\xi - \tau_2) d\xi \\ &= P(0) + \int_{-\tau_2}^0 k_t P(\zeta) B(\zeta) d\zeta\end{aligned}$$

- ▶ Similarly,

$$\begin{aligned}B_{\text{total}} &= B(0) + \int_0^{\tau_1} k_t P(\xi - \tau_1) B(\xi - \tau_1) d\xi \\ &= B(0) + \int_{-\tau_1}^0 k_t P(\zeta) B(\zeta) d\zeta\end{aligned}$$

## *Delay-differential equations*

### *Mass conservation in DDEs*

- For the initial function

$$P(t) = P_0 \quad \text{for } -\tau_2 \leq t \leq 0$$
$$B(t) = \begin{cases} 0 & \text{for } -\tau_2 \leq t < 0 \\ B_0 & \text{for } t = 0 \end{cases}$$

we get

$$P_{\text{total}} = P(0) + \int_{-\tau_2}^0 k_t P(\zeta) B(\zeta) d\zeta = P(0)$$
$$B_{\text{total}} = B(0) + \int_{-\tau_1}^0 k_t P(\zeta) B(\zeta) d\zeta = B(0)$$

## *DDEs in xppaut*

- ▶ The delayed value of a variable can be obtained by (e.g.) `delay(P, tau2)`.
- ▶ Initial functions can be specified using the `variable(0)` notation, e.g.

$$P(0)=10+4t$$

Two problems:

- ▶ This sets  $P(t)$  for  $t < 0$ . The value of  $P$  at time 0 may or may not be set correctly and frequently needs to be corrected inside `xppaut`.
  - ▶ The `init` notation cannot be used.
- ▶ A line like the following must be included in your `xppaut` input file:

`@ DELAY=1000`

The value of `DELAY` must be at least as large as the largest delay in the system.

## *DDEs in xppaut*

**Important:** The numerical integration of DDEs is tricky.  
Always try different step sizes and/or methods.