Colored extrinsic fluctuations and stochastic gene expression: Supplementary information

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Stochastic simulation algorithm with continuous and discontinuous time-dependent reaction rates

We use a time-dependent Gillespie algorithm that allows continuous and discontinuous changes in reaction rates to simulate extrinsic and intrinsic fluctuations. If the propensity of a reaction is a time-dependent $a(t)$, then the probability of the reaction occurring at a time τ is[1, 2, 3]

$$P(\tau) = a(\tau) \exp\left(-\int_0^\tau a(t)dt\right). \tag{3}$$

During a simulation we need to sample τ from $P(\tau)$. Typically, such a sample is generated from r, a sample of a random number uniformly distributed between 0 and 1, by solving[4]

$$\int_0^\tau P(t)dt = r \tag{4}$$

for τ. Inserting Eq. 3 into Eq. 4 gives

$$\int_0^\tau dt\, a(t) \exp\left(-\int_0^t a(t')dt'\right) = r \tag{5}$$

which can be integrated directly

$$1 - \exp\left(-\int_0^\tau a(t)dt\right) = r. \tag{6}$$

If r is uniformly sampled from the interval between 0 and 1, so is $1 - r$, and we can write

$$\int_0^\tau a(t)dt = \log(1/r) \tag{7}$$

which is Eq. 1 in the main paper.

Eq. 7 is valid for any $a(t)$ including one that is stochastic. To evaluate the integral of Eq. 7 for a stochastic $a(t)$, we approximate one realization of $a(t)$ with a series of step functions or a piece-wise linear function. We therefore need to consider discontinuous changes in $a(t)$.

Let $a(t)$ satisfy

$$a(t) = \begin{cases} a_<(t) & \text{for } t < t_0 \\ a_>(t) & \text{for } t > t_0 \end{cases} \tag{8}$$

then Eq. 7 implies that if r, our uniform random sample, is large, having a value r_1 say, we need to solve

$$\int_0^{\tau} dt\, a_<(t) = \log(1/r_1) \tag{9}$$

for a $\tau < t_0$. If r is small, r_2 say, we must solve

$$\int_0^{t_0} dt\, a_<(t) + \int_0^{\tau - t_0} dt\, a_>(t) = \log(1/r_2) \tag{10}$$

for a $\tau > t_0$. We can define a constant c such that

$$\int_0^{t_0} dt\, a_<(t) = \log(1/c) \tag{11}$$

where Eq. 9 implies $c \geq r_2$. Re-writing Eq. 10 then gives

$$\int_0^{\tau - t_0} dt\, a_>(t) = \log(1/r_3) \tag{12}$$

with $r_3 = r_2/c$. The new variable r_3 is a uniformly distributed random variable. We know that $r_2 \leq c$ and so r_3 has a minimum of 0 and a maximum of 1: it is uniformly distributed between 0 and 1. Eq. 12 is then the scheme used in Gillespie's first reaction method[5]: it is Eq. 7 with the new functional form of the propensity.

To simulate a discontinuous change in $a(t)$, Eq. 12 implies that we should only implement the change once the sum of the current simulation time and the next putative reaction time pass t_0. We then change $a(t)$ from $a_<(t)$ to $a_>(t)$, set the simulation time to t_0, and use Eq. 12 to sample from $a(t)$.

An alternative argument is to consider the discontinuous rate changes as implicit deterministic reactions. These reactions, however, affect rates, not numbers of molecules. The next time a reaction rate undergoes a discontinuous change should therefore be included when comparing putative reaction times.

Consequently, our algorithm is

1. Initialize the numbers of all species. Set time $t = 0$.
2. Calculate the propensity for each chemical reaction.
3. For each reaction i generate a putative next reaction time, τ_i.
4. Let μ be the reaction with minimum τ_i.
5. Let t_0 be the time for the next discontinuous change in a reaction rate. Let j be the reaction whose rate changes.
6. If $t + \tau_\mu < t_0$, then change the numbers of species appropriately for the occurrence of reaction μ. Change t to $t + \tau_\mu$. If $t + \tau_\mu > t_0$, then change the reaction rate of reaction j. Set $t = t_0$.
7. Go to step 2

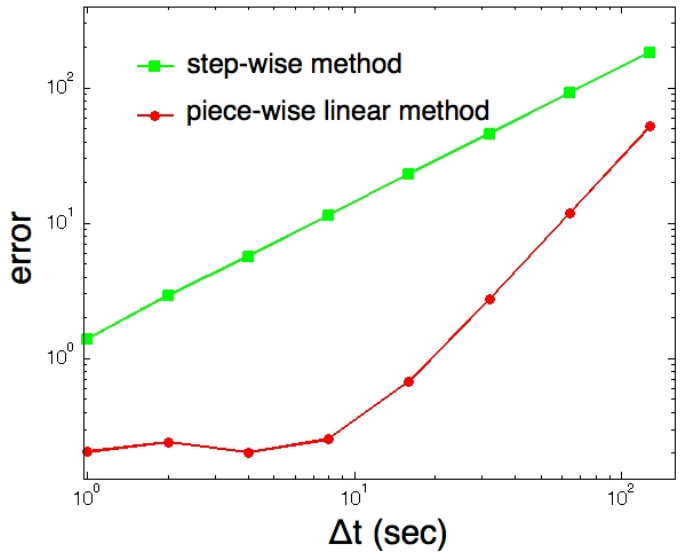

Figure 6: Comparison of the step-wise and piece-wise linear approximations for a time-dependent reaction rate. We simulate a birth-and-death, or Poisson, process for gene expression. Proteins degrade with a constant first-order rate and have a sinusoidally varying production rate. We plot the square of the difference of the mean protein number from the exact, analytical result (the solution of the deterministic mass action equation). This error is proportional to Δt for the step-wise method and to Δt^2 for the piece-wise linear approximation. Averages are over 10^4 simulation runs, but more would be needed to see the Δt^2 dependence of the error for the piece-wise linear approximation for small Δt.

This implementation is exact. We calculate putative reaction times using Eq. 7 and follow the more accurate piece-wise linear approximation (Fig. 6).

Extrinsic fluctuations in parameter values should be positive. In our simulations, we generate an Ornstein-Uhlenbeck time series using[6]

$$\frac{d\epsilon}{dt} = -\frac{\epsilon}{\tau} + \frac{\xi_0}{\tau} \tag{13}$$

where ξ_0 is a white noise source

$$\langle \xi_0(t_1)\xi_0(t_2)\rangle = 2\tau\eta_\epsilon^2\delta(t_1 - t_2) \tag{14}$$

The variable ϵ is normally distributed and has an exponentially decaying stationary autocorrelation function[1, 6]

$$C_\epsilon(t) = \eta_\epsilon^2 \mathrm{e}^{-t/\tau} \tag{15}$$

where we have taken an additional average over the initial values of ϵ, which are normally distributed with mean zero and variance η_ϵ^2. To model extrinsic fluctuations in a parameter k, we replace k by $k\mathrm{e}^\epsilon/\langle e^\epsilon\rangle$. Exponentiating ϵ ensures k is positive and the stationary distribution of k is then log-normal. Log-normal rather than normal distributions have been measured for gene expression rates[7]. We normalize k by $\langle \mathrm{e}^\epsilon\rangle = \mathrm{e}^{\eta_\epsilon^2/2}$ so that its mean is

unchanged by fluctuations. The autocorrelation function of k then obeys

$$\begin{aligned} C_{\mathrm{e}^\epsilon}(t) &= k^2\left(\mathrm{e}^{\eta_\epsilon^2 \mathrm{e}^{-t/\tau}} - 1\right) \\ &= k^2 \sum_{r=1}^{\infty} \frac{\eta_\epsilon^{2r}}{r!} \mathrm{e}^{-rt/\tau} \end{aligned} \tag{16}$$

which is dominated at long times by the timescale τ. The fluctuations of k are colored and with an approximate autocorrelation time τ. The long time behaviors of Eqs. 15 and 16 are similar and would be difficult to distinguish experimentally.

Alternatively, to simulate colored extrinsic fluctuations that have a Poisson distribution, an extrinsic variable generated by a simple birth-and-death process can be added, in the usual manner, to the Gillespie algorithm. Any chemical rate multiplied by this extrinsic variable will undergo extrinsic fluctuations and the lifetime of these fluctuations will be determined by the death rate of the extrinsic variable[8, 9]. Using this technique, it is only possible to generate extrinsic fluctuations with distributions that we know how to describe with chemical reactions. It is also not possible to generate different simulation trajectories with the same extrinsic variation.

Intrinsic and extrinsic noise

Definitions

We wish to define and measure the stochasticity in an intrinsic variable, I, which is typically the copy number of a particular protein. We consider two copies of the system of interest in the same cellular environment. Let I_1 be the intrinsic variable for the first copy of the system, I_2 be the equivalent intrinsic variable for the second copy, and let the fluctuation in a variable I be

$$\tilde{I}(t) = I(t) - \langle I(t) \rangle \tag{17}$$

where the angled brackets denoted an average over all intrinsic and extrinsic variables. Then $\tilde{I}(t)$ measures the deviation of $I(t)$ from its deterministic dynamics, i.e. the dynamics of the system in the limit of large numbers of molecules. The intrinsic noise is defined as

$$\eta_{\mathrm{int}}^2 = \frac{\left\langle (\tilde{I}_1 - \tilde{I}_2)^2 \right\rangle}{2\langle I \rangle^2} \tag{18}$$

where we have used that $\langle I_1 \rangle = \langle I_2 \rangle = \langle I \rangle$ because each system is an identical copy of the other. The extrinsic noise is the cross-correlation of $\tilde{I}_1$ and $\tilde{I}_2$,

$$\eta_{\mathrm{ext}}^2 = \frac{\langle \tilde{I}_1 \tilde{I}_2 \rangle}{\langle I \rangle^2}. \tag{19}$$

The squares of the intrinsic noise and the extrinsic noise sum to give the total noise, or the total variation in the intrinsic variable I:

$$\eta_{\mathrm{int}}^2 + \eta_{\mathrm{ext}}^2 = \eta_{\mathrm{tot}}^2 \tag{20}$$

where the total noise is the coefficient of variation of I,

$$\eta_{\rm tot}^2 = \frac{\langle \tilde{I}^2 \rangle}{\langle I \rangle^2} = \frac{1}{2}\left(\frac{\langle \tilde{I}_1^2 \rangle}{\langle I \rangle^2} + \frac{\langle \tilde{I}_2^2 \rangle}{\langle I \rangle^2} \right). \tag{21}$$

It is experimentally estimated as the average of the coefficients of variation of I_1 and I_2.

The state of the cell with its two copies of the system of interest can be represented at time t as the probability $P(\mathbf{I}_1, \mathbf{I}_2, \mathbf{E}, t)$, which is the probability that $\mathbf{I}_1$, the set of intrinsic variables for the first copy of the system, $\mathbf{I}_2$, the set for the second copy, and $\mathbf{E}$, the set of extrinsic variables, have particular values at time t. For clarity, we will integrate out of this probability all except the measured intrinsic variables, which we will write as I_1 and I_2. Similarly, we replace $\mathbf{E}$ by E through integrating out all but one of the extrinsic variables. Rather than $P(I_1, I_2, E, t)$, though, we consider the probability of the fluctuations, $P(\tilde{I}_1, \tilde{I}_2, \tilde{E}, t)$, because the fluctuations determine stochasticity.

We can verify the definitions of intrinsic, extrinsic, and total noise by confirming that the intrinsic noise is measured to be zero when the dynamics of the intrinsic variables are deterministic and that the extrinsic noise is measured to be zero when the dynamics of the extrinsic variables are deterministic. We know that the distribution $P(\tilde{I}_1, \tilde{I}_2, \tilde{E}, t)$ can be written as

$$P(\tilde{I}_1, \tilde{I}_2, \tilde{E}, t) = P(\tilde{I}_1 | \tilde{I}_2, \tilde{E}, t) P(\tilde{I}_2 | \tilde{E}, t) P(\tilde{E}, t). \tag{22}$$

and that

$$\int d\tilde{I}_1 d\tilde{I}_2 d\tilde{E}\ \tilde{I}_1 P(\tilde{I}_1, \tilde{I}_2, \tilde{E}, t) = 0 \tag{23}$$

from the definition, Eq. 17.

If the intrinsic dynamics are deterministic, then the intrinsic variables will still fluctuate because of fluctuations in the extrinsic variables, but they will always fluctuate identically:

$$P(\tilde{I}_1 | \tilde{I}_2, \tilde{E}) = \delta(\tilde{I}_1 - \tilde{I}_2) \tag{24}$$

where $\delta(x)$ is the delta function. Consequently, the intrinsic noise satisfies

$$\begin{aligned} \eta_{\rm int}^2 &\sim \int d\tilde{I}_1 d\tilde{I}_2 d\tilde{E}\ (\tilde{I}_1 - \tilde{I}_2)^2 P(\tilde{I}_1, \tilde{I}_2, \tilde{E}, t) \\ &= \int d\tilde{I}_1 d\tilde{I}_2 d\tilde{E}\ (\tilde{I}_1 - \tilde{I}_2)^2 \delta(\tilde{I}_1 - \tilde{I}_2) P(\tilde{I}_2 | \tilde{E}, t) P(\tilde{E}, t) \end{aligned} \tag{25}$$

and is zero.

If the extrinsic dynamics are deterministic, then

$$P(\tilde{E}, t) = \delta(\tilde{E}) \tag{26}$$

and the extrinsic variables will always be at their mean (deterministic) values. If there are no extrinsic fluctuations, then fluctuations in I_1 are independent of fluctuations in I_2:

$$P(\tilde{I}_1 | \tilde{I}_2, \tilde{E}, t) = P(\tilde{I}_1 | \tilde{E}, t). \tag{27}$$

Therefore, Eq. 23 becomes

$$\int d\tilde{I}_1\, \tilde{I}_1 P(\tilde{I}_1 | \tilde{E} = 0) = 0. \tag{28}$$

The extrinsic noise obeys

$$\begin{aligned}\eta^2_{\rm ext} &\sim \int d\tilde{I}_1 d\tilde{I}_2 d\tilde{E}\ \tilde{I}_1\tilde{I}_2 P(\tilde{I}_1,\tilde{I}_2,\tilde{E},t)\\ &= \int d\tilde{I}_1 d\tilde{I}_2 d\tilde{E}\ \tilde{I}_1\tilde{I}_2 P(\tilde{I}_1|\tilde{E},t)P(\tilde{I}_2|\tilde{E},t)\delta(\tilde{E})\\ &= \int d\tilde{I}_1\ \tilde{I}_1 P(\tilde{I}_1|\tilde{E}=0)\int d\tilde{I}_2\ \tilde{I}_2 P(\tilde{I}_2|\tilde{E}=0)\end{aligned} \tag{29}$$

which is zero from Eq. 28.

Slow or fast extrinsic fluctuations

In general, $P(\tilde{I}_1|\tilde{I}_2,\tilde{E}) \neq P(\tilde{I}_1|\tilde{E})$ because the current value of $\tilde{I}_2$ carries information on the history of $\tilde{E}$, over the timescale associated with variation in $\tilde{I}_2$. We must then consider $P(\tilde{I}_1,\tilde{I}_2,\tilde{E},t)$ as the distribution being interrogated by a two-color experiment. If, however, the extrinsic timescale is much faster than the intrinsic timescales of the system, then $\tilde{E}$ will appear uncorrelated in time to the intrinsic variables. Then, $P(\tilde{I}_1|\tilde{I}_2,\tilde{E}) \simeq P(\tilde{I}_1|\tilde{E})$, and we need only consider $P(\tilde{I},\tilde{E},t)$ as the experimentally relevant distribution[10]. Similarly, if there is an initial distribution of extrinsic variables so that each cell has initially a different sample from this distribution, but the extrinsic variables themselves do not change with time, then $P(\tilde{I}_1|\tilde{I}_2,\tilde{E}) = P(\tilde{I}_1|\tilde{E})$. In both cases, there is no finite timescale associated with extrinsic fluctuations. If extrinsic fluctuations have a significant lifetime, then we must consider $P(\tilde{I}_1,\tilde{I}_2,\tilde{E},t)$.

Mathematical modeling

Langevin theory

We use Langevin theory to model both intrinsic and extrinsic fluctuations. To include intrinsic fluctuations, we add white noise terms to the deterministic equations describing Fig. 1a. If D is the number of promoters in the active state, M the number of mRNAs, and A the number of proteins, we have

$$\begin{aligned}\frac{dD}{dt} &= k_0 - (k_0+k_1)D + \xi_1\\ \frac{dM}{dt} &= v_0 D - d_0 M + \xi_2\\ \frac{dA}{dt} &= v_1 M - d_1 A + \xi_3\end{aligned} \tag{30}$$

where the ξ_i are stochastic variables that satisfy[11]

$$\begin{aligned}\langle\xi_1(t_1)\xi_1(t_2)\rangle &= 2k_1 D_s\delta(t_1-t_2)\\ \langle\xi_2(t_1)\xi_2(t_2)\rangle &= 2d_0 M_s\delta(t_1-t_2)\\ \langle\xi_3(t_1)\xi_3(t_2)\rangle &= 2d_1 A_s\delta(t_1-t_2)\end{aligned} \tag{31}$$

with all the cross-correlations $\langle \xi_i(t_1)\xi_j(t_2)\rangle = 0$ when i is not equal to j. Non-zero cross-correlations only arise from second-order reactions. D_s, M_s, and A_s are steady-state concentrations.

To include extrinsic fluctuations, we add the stochastic variable ϵ whose dynamics satisfy the Ornstein-Uhlenbeck process of Eq. 13. The white noise ξ_0 is uncorrelated with any other ξ_i. We use ϵ to add extrinsic fluctuations to any parameter in the model of Fig. 1a. For example, we let $v_0 \to v_0 \mathrm{e}^{\epsilon}/\langle \mathrm{e}^{\epsilon}\rangle$ to include extrinsic fluctuations in transcription. Nevertheless, we need to linearize this expression to make the calculations tractable and use $v_0 \to v_0(1+\epsilon)$. Our approach is therefore only valid when extrinsic fluctuations are small. With this definition, v_0 has a coefficient of variation of η_ϵ^2 and has an autocorrelation time of τ (Eq. 15).

Mathematically, colored extrinsic fluctuations in one parameter adds another variable, ϵ, to Eqs. 30. Multiple correlated extrinsic fluctuations acting on different parameters of the system correspond to the same ϵ changing the relevant parameters. Multiple uncorrelated extrinsic fluctuations require an ϵ_i for each uncorrelated fluctuation. The solution of the system with intrinsic and extrinsic fluctuations is therefore given by the general solution already found for any linear system with intrinsic fluctuations[11]. We use this solution to calculate the coefficient of variation of protein numbers.

The intrinsic noise satisfies[12]

$$\eta_{\mathrm{int}}^2 = \frac{1}{A_s} + \frac{d_1}{d_0+d_1}\left[\frac{1}{M_s} + \frac{d_0(d_0+d_1+k_0+k_1)}{(d_0+k_0+k_1)(d_1+k_0+k_1)}\eta_D^2\right] \tag{32}$$

and has contributions from translation, transcription, and the stochastic transitioning of the promoter between active and inactive states ($\eta_D^2 = \frac{1-D_s}{D_s}$). With v_1 or d_1 in Fig. 1a fluctuating, we find that

$$\eta_{\mathrm{ext}}^2 = \frac{d_1\tau}{1+d_1\tau}\eta_\epsilon^2, \tag{33}$$

while if v_0 or d_0 fluctuates, η_{ext} obeys

$$\eta_{\mathrm{ext}}^2 = \frac{d_1}{d_0+d_1}\cdot\frac{d_0\tau[1+(d_0+d_1)\tau]}{(1+d_0\tau)(1+d_1\tau)}\eta_\epsilon^2. \tag{34}$$

Similar, although more complex, expressions result with k_0 or k_1 fluctuating. The extrinsic noise in proteins numbers is determined both by the coefficient of variation of the fluctuating parameter, η_ϵ, and its autocorrelation time, τ.

We can do similar calculations if two parameters in Fig. 1a fluctuate. If these extrinsic fluctuations are uncorrelated, we find

$$(\eta_{\mathrm{ext}}^{(i,j)})^2 = (\eta_{\mathrm{ext}}^{(i)})^2 + (\eta_{\mathrm{ext}}^{(j)})^2 \tag{35}$$

where $\eta_{\mathrm{ext}}^{(i,j)}$ is the extrinsic noise of protein numbers when parameters labeled by i and j fluctuate and $\eta_{\mathrm{ext}}^{(i)}$ is the extrinsic noise when only the parameter labeled with i fluctuates. With correlated extrinsic fluctuations, we find that $(\eta_{\mathrm{ext}}^{(i,j)})^2 \ll (\eta_{\mathrm{ext}}^{(i)})^2 + (\eta_{\mathrm{ext}}^{(j)})^2$ if the two fluctuating parameters have opposing effects on protein numbers. For example, if we have correlated fluctuations in d_0 and v_1,

$$\eta_{\mathrm{ext}}^2 = \frac{d_1}{d_0+d_1}\cdot\frac{d_1\tau}{(1+d_1\tau)(1+d_0\tau)}\eta_\epsilon^2 \tag{36}$$

which vanishes as τ increases, unlike Eq. 33. If the two parameters affect protein numbers similarly, $(\eta_{\text{ext}}^{(i,j)})^2 \gg (\eta_{\text{ext}}^{(i)})^2 + (\eta_{\text{ext}}^{(j)})^2$. For example, if we have correlated fluctuations in v_0 and v_1,

$$\eta_{\text{ext}}^2 = \frac{d_1}{d_0 + d_1} \cdot \frac{d_1\tau + 4d_0\tau[1 + \tau(d_0 + d_1)]}{(1 + d_1\tau)(1 + d_0\tau)}\eta_\epsilon^2 \tag{37}$$

which tends to four times the noise generated by fluctuations in v_1 alone as τ increases.

We repeated this analysis for a negatively auto-regulated network. As before, if both parameters have similar effects on mean protein numbers, correlated extrinsic fluctuations combine constructively. While if both parameters have opposing effects on mean protein numbers, they combine destructively.

The unified colored noise approximation

Our Langevin approach is linear and is unable to reproduce the changes in the protein mean or in intrinsic noise that are caused by extrinsic fluctuations. Such effects are non-linear. We are not aware of a general analytical method to study the complete, non-linear model, but the unified colored noise approximation has been proposed to describe multiplicative colored noise in a system with only one dynamical variable[13]. This theory is exact for both $\tau = 0$ and $\tau = \infty$.

We consider a reduced model of Fig. 1a that ignores the dynamics of mRNA and the promoter, but incorporates colored extrinsic fluctuations in the protein degradation rate, d_1:

$$\frac{dA}{dt} = k - d_1(1 + \epsilon)A + \xi \tag{38}$$

where $k = v_1 M_s$ and is assumed not to fluctuate. Both ξ and ϵ are stochastic variables. Intrinsic fluctuations are described by ξ, which is a white noise term, and extrinsic fluctuations by ϵ, which obeys Eq. 13 as before. If we ignore intrinsic fluctuations by setting $\xi = 0$, the steady-state distribution of proteins obeys

$$P(A = a) \sim \frac{k\tau + a}{d_1} \cdot a^{-2-\frac{1}{d_1\tau\eta_\epsilon^2}} \cdot e^{\frac{-k[k\tau + 2a(1-d_1\tau)]}{2d_1^2\tau a^2\eta_\epsilon^2}} \tag{39}$$

which has a complex mixing of the intrinsic (d_1) and extrinsic (τ) timescales. The mean of this distribution depends on the timescale (τ) and strength (η_ϵ^2) of the extrinsic fluctuations (Fig. 2c and Fig. 2d). Nevertheless, its width is less than that seen in simulations because we have ignored intrinsic fluctuations. Using an extension to the unified colored noise approximation[14], we can include intrinsic fluctuations and can explicitly show the interdependence of intrinsic and extrinsic fluctuations (results not shown).

Simulation specifications

We used the *Facile* compiler and *EasyStoch* [15] to run our reactions. Both are freely available at `www.cnd.mcgill.ca/~swain`. We include the input files for Figs. 1–5. In each file, the EQN section describes the network, giving each chemical reaction followed by its forward

and backward rates. These rates are in s^{-1} for first order reactions and in $M^{-1}s^{-1}$ for second-order reactions. The INIT section provides the initial values in numbers of molecules for all chemical species that are not initially zero.

Fig. 1, Fig. 2, and Fig. 3

The model of Fig. 1a. Degradation is denoted by the `null` state and `D_off` represents the number of promoter molecules in the inactive state. For Fig. 3 a random set of parameters is used as explained in Materials and methods. Comments are preceded with a hash sign.

```
EQN
D <-> D_off;  k0 = 0.03; k1 = 0.005
# expression of protein A
D -> D + M;   v0 = 0.07
M -> null;    d0 = 0.005
M -> M + A;   v1 = 0.2
A -> null;    d1 = 0.0004

INIT
D = 1
```

Fig. 4

A negatively auto-regulation network based on the model of Fig. 1a. We also specify the cell volume in liters to simulate second-order reactions.

```
EQN
# negative autoregulation
D <-> D_off;       k0 = 0.03; k1 = 0.005
D_off + A <-> DA;  l1 = 3.2e5; l0 = 0.02
# expression of protein A
D -> D + M;        v0 = 0.07
M -> null;         d0 = 0.005
M -> M + A;        v1 = 0.2
A -> null;         d1 = 0.0004

INIT
D = 1
CONFIG
compartment_volume = 1.66e-15
```

Fig. 5c

A coherent type 1 feedforward loop.

```
EQN
# gene Y is activated by protein X
D_Y + X <-> D_Y_X;          l0 = 1e5; l1 = 0.5
# expression of gene Y
D_Y_X -> D_Y_X + M_Y;       v0 = 0.07
M_Y -> null;                d0 = 0.005
M_Y -> M_Y + Y;             v1 = 0.2
Y -> null;                  d1 = 4e-4
# gene Z is activated by proteins X and Y together
D_Z + X <-> D_Z_X;          l2 = 1e5; l3 = 0.15
D_Z + Y <-> D_Z_Y;          l2; l3
D_Z_X + Y <-> D_Z_X_Y;      l2; l3
D_Z_Y + X <-> D_Z_X_Y;      l2; l3
# expression of gene Z
D_Z_X_Y -> D_Z_X_Y + M_Z;   v0
M_Z -> null                 d0
M_Z -> M_Z + Z;             v1
Z -> null;                  d1

INIT
X = 1000
D_Y = 1
D_Z = 1
CONFIG
compartment_volume = 1.66e-15
```

Fig. 5d

Incoherent type 1 feedforward loop.

```
EQN
# gene Y is activated by protein X
D_Y + X <-> D_Y_X;       l0 = 1e5; l1 = 0.5
# expression of gene Y
D_Y_X -> D_Y_X + M_Y;    v0 = 0.07
M_Y -> null;             d0 = 0.005
M_Y -> M_Y + Y;          v1 = 0.2
Y -> null;               d1 = 4e-4
# gene Z is activated by protein X
D_Z + X <-> D_Z_X;       l2 = 1e5; l3 = 0.5
# gene Z is repressed by protein Y
D_Z + Y <-> D_Z_Y;       l2; l4 = 0.1
D_Z_X + Y <-> D_Z_X_Y;   l2; l4
D_Z_Y + X <-> D_Z_X_Y;   l2; l3
# basal constitutive expression of gene Z
```

```
D_Z -> D_Z + M_Z;       v0_b = 0.01
# expression of gene Z
D_Z_X -> D_Z_X + M_Z;   v0
M_Z -> null;            d0
M_Z -> M_Z + Z;         v1
Z -> null;              d1

INIT
X = 1000
D_Y = 1
D_Z = 1
CONFIG
compartment_volume = 1.66e-15
```


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