Notes on modeling of growth-regulation interactions in the cAMP system

Martijn Wehrens

September 29, 2016

Chapter 1

Modeling the noise transmission

1.1 Ornstein-Uhlenbeck fluctuations model

1.1.1 The model assumptions

The ODEs formulated below are based on the model diagram displayed in Fig. 1.1. Fig. 1.1.A displays the drawing as proposed in Kiviet et al, Fig. 1.1.B displays a more technical version, which directly reflects my interpretation of the model.

1.1.2 Implicit noise equations

Initially, I used the following model were ODEs are numerically solved:

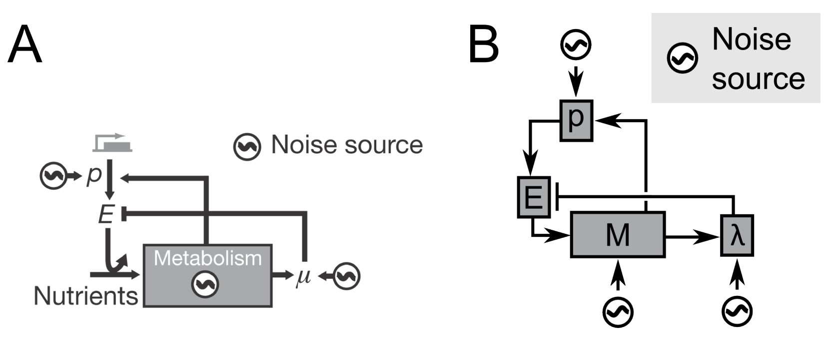

Figure 1.1: Model as proposed by Kiviet 2014 et al. (A) Original diagram as printed in Kiviet 2014 et al. [3]. (B) More technical diagram stating the relations between parameters of interest (gray boxes), and noise sources Γ_P, Γ_M, and Γ_λ. Arrows indicate how ODEs that describe the parameters of interest are coupled.

$$
\begin{aligned}
\dot{M} = &-\frac{(M-M_0)}{\tau} \\
&+c_M \cdot \Gamma_M \\
&+T_{M\leftarrow E} \cdot c_M \cdot (\frac{E}{E_0}-1)
\end{aligned} \tag{1.1}
$$

$$
\begin{aligned}
\dot{\lambda} = &-\frac{(\lambda-\lambda_0)}{\tau_\lambda} \\
&+c_\lambda \cdot \Gamma_\lambda \\
&+T_{\lambda\leftarrow\ M} \cdot c_\lambda \cdot (\frac{M}{M_0}-1)
\end{aligned} \tag{1.2}
$$

$$
\begin{aligned}
\dot{P} = &-\frac{(P-P_0)}{\tau_P} \\
&+c_\lambda \cdot \Gamma_\lambda \\
&+T_{P\leftarrow M} \cdot c_P \cdot (\frac{M}{M_0}-1) \\
&+R_{P\leftarrow M} \cdot c_P \cdot (\frac{M}{M_0}-1)
\end{aligned} \tag{1.3}
$$

$$
\dot{E} = P - \lambda E \tag{1.4}
$$

Where M describes the state of the metabolism, λ is the growth rate, P is the production rate, E is the amount of enzyme, τ is a dampening term (X_0 is the equilibrium value), $T_{X\leftarrow Y}$ is the noise transmission constant from X towards Y, c_X is a constant that sets the size of the fluctuations, Γ_X is a white noise source. $R_{X\leftarrow Y}$ indicates a regulatory interaction, an addition to the model by me, but this notation is currently just cosmetical, as $T_{\text{effective}} = T + R$. This model assumes all parameters have an average value from which fluctuations deviate, but always return. Hence the dampening terms. With respect to transmission, I furthermore rescale the absolute value of the noise to be comparable to the target noise (hence the M_0^{-1} and c_X terms in combination with the $T_{X\leftarrow Y}$ term).

This is similar to the model that Philipe Nghe had in Kiviet et al. [3], which was inspired by [1] (see supplement). A difference between my equations, the Nghe equations and the Dunlop equations lies in the dampening terms (those containing τ, β or μ_E). In my model noise is effected through the ODE, and dampening occurs on the parameter of interest. In Dunlop et al., there are two dampening terms, one specifically dampening the noise and a second term dampening the parameters of interest. It seems also Nghe takes the latter approach, dampening being effected through the $(-\beta_X \cdot N_X)$ term and the μ_E parameter (see later for a more involved discussion on these parameters).

The correlations between these equations can be found by linearizing them, writing the correlations in Fourier space, and back-transforming them using residue integration techniques. This document currently does not fully explores this, but this will partially be discussed later. First, a comparison with the Nghe model is made.

1.2 Separate noise equations

Both Nghe and Dunlop define separate ODEs for the noise terms:

$$\dot{N}_X = \sqrt{C_X} \cdot \Gamma_X - N_X/\tau, \tag{1.5}$$

though their notation might be slightly different (I used Daniel Gillespie's notation [2]; a capital C is used here to follow Gillespie's square root notation, $\sqrt{C_X} = c_x$). With for our case X equaling λ, M or P. Note that $\tau^{-1} = \beta$ (β is used in Nghe and Dunlop).

Not so relevant for our case, but noteworthy, is that in the Dunlop model, which models a completely different process than the one described here [1], the *solutions* of the ODEs describing the noise are plugged into the ODEs describing the protein dynamics. This leads to an additional memory effect. That is:

$$\dot{X} = N_X + F(X) + X/\tau, \tag{1.6}$$

with $F(X)$ some arbitrary function of X. Note that the N_X function also contains a τ term (see Eq. 1.5), which is effectively integrated, thus leading to effects of the fluctuations much longer timescales than τ. This effect is (partially) countered by the third term in Eq. 1.6, which also contains the τ term.

1.3 Nghe model

The Nghe model does not seem to have this integration of noise, but instead defines:

$$\dot{E} = P - \lambda E \tag{1.7}$$

(which is the same in my model), and:

$$\frac{\delta\mu}{\mu_0} = T_{\mu\leftarrow E}\frac{\delta E}{E_0} + T_{\mu\leftarrow G}N_G + N_\mu, \tag{1.8}$$

$$\frac{\delta p}{E_0\mu_0} = T_{E\leftarrow E}\frac{\delta E}{E_0} + T_{E\leftarrow G}N_G + N_E, \tag{1.9}$$

were a linearization was performed, i.e. $X = X_0 + \delta X$. Eq. 1.8 and Eq. 1.9 were already linear, but Eq. 1.7 is non-linear, and is thus rewritten into

$$\frac{\delta\dot{E}}{E_0\mu_0} + \frac{\delta E}{E_0} = \frac{\delta p}{E_0\mu_0} + T_{E\leftarrow\mu}\frac{\delta\mu}{\mu_0} \tag{1.10}$$

where Eq. 1.8 and Eq. 1.9 were plugged in directly in the linearization of 1.7. There are currently a few things unclear about Eq. 1.8 and Eq. 1.9 (respectively Eq. 3 and 4 in the Kiviet et al. manuscript):

- It seems that the transmission terms $T_{X \leftarrow Y}$ state how the parameter of interest (X) is affected by another parameter of interest (Y), however, for this to be true, the left-hand side parameter should match the first parameter in the subscript of T. E.g. how can a $T_{E \leftarrow G}$ term appear in the equation for δp and moreover, what does the term $T_{E \leftarrow E}$ mean?
- It is not clear to me how these formulae relate to the diagram that was drawn (see Fig. 1.1). Why is E directly effecting μ? Should there not also be a metabolism term G or δG? Also why does the formula for δp contain transmission from E (assuming $T_{E \leftarrow E}$ was a type and should have been $T_{p \leftarrow E}$)? Why does the formula for δp contain a noise term for E (ie. N_E)?
- These are not ODEs (which would seem more natural to me), probably this is intended this way, and the relationship between the parameters is defined as such. (And could be derived from ODEs.)

In any case, given that noise and other parameters are related in terms of parameters (not derivatives), the following formulae are probably underlying the Nghe model:

$$\begin{aligned} \dot{M} =& \dot{N}_M \\ &+ T_{M \leftarrow E} \cdot c_M \cdot (\frac{E}{E_0} - 1) \end{aligned} \tag{1.11}$$

$$\begin{aligned} \dot{\lambda} =& \dot{N}_\lambda \\ &+ T_{\lambda \leftarrow M} \cdot c_\lambda \cdot (\frac{M}{M_0} - 1) \end{aligned} \tag{1.12}$$

$$\begin{aligned} \dot{P} =& \dot{N}_P \\ &+ T_{P \leftarrow M} \cdot c_P \cdot (\frac{M}{M_0} - 1) \\ &+ R_{P \leftarrow M} \cdot c_P \cdot (\frac{M}{M_0} - 1) \end{aligned} \tag{1.13}$$

Where the normalizations by X_0 were left out again. Note however, that this results in the absence of dampening terms on the parameters X themselves, which leads to non-steady state behavior of the parameters. The term X/τ could be added to each of the equations to resolve this issue; the term $-N_X/\tau$ from the noise ODEs could then be dropped. Note that a μ_E term appears eventually in Nghe's equations, which might play the role of a second dampening term.

1.4 Obtaining the cross correlations

1.4.1 Obtaining solutions in Fourier space

How do we get the cross correlations? A way to define correlations is[1]:

[1] From Wikipedia, https://en.wikipedia.org/wiki/Cross-correlation and Weisstein, Eric W. "Cross-Correlation Theorem." From MathWorld–A Wolfram Web Resource. http://mathworld.wolfram.com/Cross-CorrelationTheorem.html

$$R_{f,g}(\tau) = f \star g = \int_{\tau=\infty}^{\infty} \bar{f}(\tau) g(t+\tau) \delta\tau \tag{1.14}$$

With the $\bar{f}$ denoting the complex conjugate. This is equal to the convolution of $f^*(-t)$ and $g(t)$,

$$f \star g = f * (-t) * g. \tag{1.15}$$

It can be derived that:

$$\mathcal{F}(f \star g) = \overline{\mathcal{F}(f)} \mathcal{F}(g). \tag{1.16}$$

This property can be exploited to find the cross correlation that we are interested in:

$$R_{\mu,E}(\tau) = \mathcal{F}^{-1}\left(\overline{\mathcal{F}(\mu)} \mathcal{F}(E)\right). \tag{1.17}$$

First we find the solutions to the ODEs in Fourier space:

$$\begin{aligned} \mathcal{F}\left(\dot{E}\right) =& \mathcal{F}\left(P - \lambda E\right) \\ i\omega \tilde{E} =& \tilde{P} - \tilde{\lambda} \tilde{E} \end{aligned} \tag{1.18}$$

$$\tilde{E} = \frac{1}{i\omega + \tilde{\lambda}} \tilde{P} \tag{1.19}$$

For Eq. 1.5 the solution in Fourier space is:

$$\tilde{N}_X = \frac{\sqrt{c_x}}{i\omega - 1/\tau} \tilde{\Gamma}_x \tag{1.20}$$

which however will not be directly used to solve Eq. 1.1-1.4. With regard to Eq. 1.1-1.3, the solutions in general terms can be found from taking the Fourier transform:

$$i\omega \tilde{X} = -\frac{\tilde{X} - X_0}{\tau_X} + c_X \tilde{\Gamma}_X + T_{X \leftarrow Y} c_X (\frac{\tilde{Y}}{X_0} - 1) \tag{1.21}$$

which, solving for X gives:

$$\tilde{X} = \left(i\omega + \frac{1}{\tau_X}\right)^{-1} \left(\frac{X_0}{\tau_X} + c_X \tilde{\Gamma}_X + T_{X \leftarrow Y} c_X (\frac{\tilde{Y}}{Y_0} - 1)\right), \tag{1.22}$$

X being either λ, M or P. The solution for E in Fourier space (i.e. to Eq. 1.4) without P or λ terms is very involved. This can be seen by plugging Eq. 1.22 into Eq. 1.18, which results in:

$$\begin{aligned}i\omega\tilde{E} = &\left(i\omega + \frac{1}{\tau_P}\right)^{-1}\left(\frac{P_0}{\tau_P} + c_P\tilde{\Gamma}_P + T_{P\leftarrow M}c_P(\frac{\tilde{M}}{M_0} - 1)\right)\\ &- \left(i\omega + \frac{1}{\tau_\lambda}\right)^{-1}\left(\frac{\lambda_0}{\tau_\lambda} + c_\lambda\tilde{\Gamma}_\lambda + T_{\lambda\leftarrow M}c_\lambda(\frac{\tilde{M}}{M_0} - 1)\right)\tilde{E}\end{aligned} \tag{1.23}$$

Where M is defined as:

$$\tilde{M} = \left(i\omega + \frac{1}{\tau_M}\right)^{-1}\left(\frac{M_0}{\tau_M} + c_M\tilde{\Gamma}_M + T_{M\leftarrow E}c_M(\frac{\tilde{E}}{E_0} - 1)\right) \tag{1.24}$$

Plugging Eq. 1.24 into Eq. 1.23 results in an equation where the only time-dependent parameter is E. Solving that formula for E gives a very involved formula, which is not displayed here.

1.4.2 Actually getting the cross-correlations

As Dunlop et al. point out, we are now looking at the expectation values of the correlation functions (since we're talking about noise), so in general terms:

$$\langle R_{X,Y}(\tau)\rangle = \left\langle \mathcal{F}^{-1}\left[\overline{\mathcal{F}(X)}\mathcal{F}(Y)\right]\right\rangle \tag{1.25}$$

1.5 Notes

Note that Philippe Nghe's scripts can be found at:

```
\\storage01\data\AMOLF\groups\tans-group\Former-Users\
Nghe\Noise_Growth\matlab3
```

Bibliography

[1] Mary J Dunlop, Robert Sidney Cox, Joseph H Levine, Richard M Murray, and Michael B Elowitz. Regulatory activity revealed by dynamic correlations in gene expression noise. *Nature genetics*, 40(12):1493–8, dec 2008.

[2] Dt Gillespie. Exact numerical simulation of the Ornstein-Uhlenbeck process and its integral. *Physical review. E, Statistical physics, plasmas, fluids, and related interdisciplinary topics*, 54(2):2084–2091, aug 1996.

[3] Daniel J. Kiviet, Philippe Nghe, Noreen Walker, Sarah Boulineau, Vanda Sunderlikova, and Sander J. Tans. Stochasticity of metabolism and growth at the single-cell level. *Nature*, sep 2014.