Separating Intrinsic from Extrinsic Fluctuations in Dynamic Biological Systems (Supplementary Information)

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This supplementary material presents the proofs of the mathematical results presented in the main text.

Example environmental state decomposition:

The discrepancy between a static decomposition (cf. Eq. $\mathbf{3}$ of the main text) and intrinsic and extrinsic noise contributions in dynamical systems is illustrated by the example reaction scheme $\mathbf{4}$ (main text). Making use of the fact that $P(z)$ follows a Poisson distribution satisfying $P(z+1) = P(z) \times \lambda_z/(\beta_z(z+1))$ we can derive the following recurrence relation for $\langle x|z\rangle = \sum_x xP(x,z)/P(z)$ from the master equation

$$\lambda_x z = \beta_x \langle x|z\rangle - \beta_z z\left(\langle x|z-1\rangle - \langle x|z\rangle\right) - \lambda_z\left(\langle x|z+1\rangle - \langle x|z\rangle\right) \quad .$$

Substitution verifies that this equation has a simple solution of the form $\langle x|z\rangle = A + Bz$ and we find

$$\langle x|z\rangle = \frac{\beta_x}{\beta_x+\beta_z}\left(\frac{\lambda_x\lambda_z}{\beta_x\beta_x} + \frac{\lambda_x}{\beta_x}z\right) \quad ,$$

which also satisfies the additional conditions that determine the solution to a second order recurrence relation: $\sum_x \langle x|z\rangle P(z) = \langle x\rangle$ and $\langle x|0\rangle = \langle x|1\rangle\lambda_z/(\lambda_z+\beta_x)$ (from evaluating the master equation at the $z=0$ edge). Averaging over the extrinsic distribution then leads to

$$\langle\langle x|\mathbf{Z}\rangle^2\rangle \equiv \sum_z \langle x|z\rangle^2 P(z) = \langle x\rangle^2\left(1 + \frac{1}{\langle z\rangle}\frac{\tau_z}{\tau_x+\tau_z}\right) \quad ,$$

and the result of Eq. $\mathbf{6}$ (main text) for $\langle\sigma^2_{X|Z}\rangle = \langle\langle x|\mathbf{Z}\rangle^2\rangle - \langle\langle x|\mathbf{Z}\rangle\rangle^2$ follows.

Periodically changing environments:

Introducing conditional averages for a given environmental time trace $\mathbf{Z}[0,t^*]$ that ends at a specific phase t^*, and then averaging over all phases t^* allows us to re-write the conditional averages in Eq. $\mathbf{9}$ (main text): $\langle\langle X_t|\mathbf{Z}[0,t]\rangle\rangle_{\mathbf{Z}[0,t]} = \langle\langle\langle X_t|\mathbf{Z}[0,t^*]\rangle\rangle_{\mathbf{Z}[0,t^*]}\rangle_{t^*}$ where the subscripts denote the variable we average over. Using those conditional averages and making use of $\langle\langle X_t|\mathbf{Z}[0,t^*]\rangle\rangle_{\mathbf{Z}[0,t^*]} = \langle X_t|t^*\rangle$ we can apply the law of total variance to the extrinsic noise

$$\begin{aligned}\sigma^2_{\rm ext} = \; & \langle \underbrace{\langle\langle X_t|\mathbf{Z}[0,t^*]\rangle^2\rangle_{\mathbf{Z}[0,t^*]} - \langle\langle X_t|\mathbf{Z}[0,t^*]\rangle\rangle^2_{\mathbf{Z}[0,t^*]}}_{\sigma^2_{\rm ext}(t^*)} \rangle_{t^*} \\ & + \underbrace{\langle\langle\langle X_t|\mathbf{Z}[0,t^*]\rangle\rangle^2_{\mathbf{Z}[0,t^*]}\rangle_{t^*} - \langle\langle\langle X_t|\mathbf{Z}[0,t^*]\rangle\rangle_{\mathbf{Z}[0,t^*]}\rangle^2_{t^*}}_{\sigma^2_{\langle X_{t^*}|t^*\rangle}} \quad ,\end{aligned}$$

and the result of Eq. $\mathbf{9}$ (main text) follows. Because the two reporters are independent when conditioned on an environmental history $\mathbf{Z}[0,t^*]$ we furthermore have

$$\begin{aligned}\sigma^2_{\mathsf{ext}}(t^*) &= \langle\langle X_t Y_t|\mathbf{Z}[0,t^*]\rangle\rangle_{\mathbf{Z}[0,t^*]} - \langle\langle X_t|\mathbf{Z}[0,t^*]\rangle\rangle^2_{\mathbf{Z}[0,t^*]} \\ &= \underbrace{\langle X_t Y_t|t^*\rangle - \langle X_t|t^*\rangle\langle Y_t|t^*\rangle}_{\mathrm{Cov_{sync}}(x,y;t^*)} \quad .\end{aligned}$$

Modeling intrinsic noise – additive environments:

By considering $\sum_{\mathbf{x},\mathbf{y}} x^2 \mathrm{d}P/\mathrm{d}t$ we find that for intrinsically linear systems the time evolution of the conditional covariance matrix $C_{ij} \equiv \langle X_{i,t}X_{j,t}|\mathbf{Z}[0,t]\rangle - \langle X_{i,t}|\mathbf{Z}[0,t]\rangle\langle X_{j,t}|\mathbf{Z}[0,t]\rangle$ follows

$$\frac{\mathrm{d}C}{\mathrm{d}t} = JC + (JC)^T + B \quad ,$$

with Jacobian $J_{ij} = \sum_k s_{ki}\mathrm{d}r_k/\mathrm{d}x_j$ and diffusion matrix $B_{ij} = \sum_k r_k(\langle \mathbf{X}_t|\mathbf{Z}[0,t]\rangle, \mathbf{z}(t))s_{ki}s_{kj}$. For systems subject to additive environmental influences the Jacobian matrix is constant, which means that by taking time averages we obtain an equation for the covariance matrix: $0 = J\langle C\rangle + (J\langle C\rangle)^T + \langle B\rangle$. Replacing the fluctuating rate constants of the original system with their averages leads to a system with a constant diffusion matrix given by $\langle B\rangle$ while leaving the Jacobian unchanged. Its covariance matrix therefore satisfies the same equation as C. Thus the intrinsic noise $\sigma^2_{\mathrm{int}} \equiv \langle C_{nn}\rangle$ can indeed be modeled by replacing fluctuating rates with their averages and thereby eliminating the extrinsic variability from systems linear in intrinsic variables and subject to additive environmental noise.

Modeling intrinsic noise – multiplicative environments:

For the system described in reaction scheme $\mathbf{11}$ (main text) the conditional average and the conditional variance follow

$$\begin{aligned}\frac{\mathrm{d}\langle \mathbf{X}_t|\mathbf{Z}[0,t]\rangle}{\mathrm{d}t} &= \lambda(\mathbf{z}(t)) - \beta(\mathbf{z}(t))\langle \mathbf{X}_t|\mathbf{Z}[0,t]\rangle \\ \frac{\mathrm{d}\sigma^2_{X_t|\mathbf{Z}[0,t]}}{\mathrm{d}t} &= \lambda(\mathbf{z}(t)) + \beta(\mathbf{z}(t))\langle \mathbf{X}_t|\mathbf{Z}[0,t]\rangle - 2\beta(\mathbf{z}(t))\sigma^2_{X_t|\mathbf{Z}[0,t]} \quad .\end{aligned}$$

Substituting the ansatz $f(t) = \sigma^2_{X_t|\mathbf{Z}[0,t]} - \langle \mathbf{X}_t|\mathbf{Z}[0,t]\rangle$ we obtain $\mathrm{d}f/\mathrm{d}t = -2\beta(\mathbf{z}(t))f$ and therefore $f(t) \sim \exp[-2\int \beta(\mathbf{z}(t))\mathrm{d}t]$ which tends to zero as $t \to \infty$. Hence the time averages satisfy $\langle \sigma^2_{X_t|\mathbf{Z}[0,t]}\rangle = \langle\langle \mathbf{X}_t|\mathbf{Z}[0,t]\rangle\rangle$. Replacing $\beta(\mathbf{z})$ with the constant $\langle \beta(\mathbf{z})x\rangle/\langle x\rangle$ and replacing $\lambda(\mathbf{z})$ with $\langle \lambda(\mathbf{z})\rangle$ removes the effect of environmental variability while preserving the system average. This process thus eliminates the influence of environmental variability while leading to a system whose fluctuations model the intrinsic noise.