I. Deterministic Description

Enzymatic Futile Cycle. In the deterministic case, the enzymatic futile cycle system, Fig. 1, has three mass-conservation constraints,

$$X(t) + C_+(t) + X^*(t) + C_-(t) = \widetilde{X}_0 = Const\,, \qquad \textbf{[S1]}$$

where $C_{+/-}$ refers to the fraction of the enzyme being tied in the enzyme–substrate complex, e.g., $C_{+/-} = E_{+/-} \circ X^{(*)}$. Additionally,

$$\begin{aligned} E_+(t) + C_+(t) &= E_+^T(t) = E_+ = Const, \quad \text{and} \\ E_-(t) + C_-(t) &= E_-^T(t) = E_- = Const, \end{aligned} \qquad \textbf{[S2]}$$

where $E_{+/-}$ is a constant total enzyme level.

Using constraints in Eqs. **S1** and **S2**, classical mass-action kinetics equations describing the deterministic time evolution of the signal species concentrations in the quasi-steady-state regime could be written in the form of Michaelis–Menten (MM) approximation as (1-3):

$$\begin{aligned} dC_{+/-} \to 0 \quad &\overset{[S1]}{\Rightarrow} \quad X + X^* = X_0 = Const, \\ dX^* = -A(X)\,dt = -dX \quad &\text{with} \quad A(X) = -k_+ C_+(X,t) + k_- C_-(X^*,t), \end{aligned} \qquad \textbf{[S3]}$$

where $A(X)$ corresponds to the deterministic drift,

$$C_+(X,t) = \frac{E_+ X}{K_+ + X}, \quad \text{and} \quad C_-(X^*,t) = \frac{E_- X^*}{K_- + X^*} = \frac{E_-(X_0 - X)}{K_- + X_0 - X}, \qquad \textbf{[S4]}$$

$k_{+/-}$ are the catalytic constants of the enzyme (the complex to product reaction rates), and $K_{+/-}$ are the Michaelis constants for the substrate reaction with $E_{+/-}^T << X_0 + K_{+/-}$.

Note that the deterministic stationary response curve, R_0, given in Eq. **1** and obtained from Eqs. **S3** and **S4**, is quadratic, i.e., at most two solutions are possible and at most one is stable. That is, the deterministic description of the system predicts a monostable behavior for any set of parameters. In fact, this system has a unique positive real root, $X_{ss}(E_+)$, satisfying $X_{ss} \le X_0$, which could be ascertained by, for example, noting that $A'(X) < 0$. That is, every steady state is a down-going root of $A(X)$, i.e., stable, which in turn implies that such a root is unique on any interval for which $A(X)$ is

continuous, including $X \le X_0$. The solution has a characteristic sigmoidal shape that approaches step function for certain parameters [resulting in zero-order ultrasensitivity (ZOU)]. An example of such a family of curves is shown in Fig. 6.

Extended System. In the numerical analysis section of our work we consider an extended chemical system, for which basic enzymatic futile cycle reactions (Expression **7**) (Fig. 1) are augmented with the external driver reaction set (Expression **8**). To validate that the effects we are proposing to numerically substantiate are indeed stochastic in nature, we briefly consider the deterministic description of this extended reaction system.

The chemical kinetic equations for this system can be readily written as

$$\begin{aligned} &\frac{dX^{\pm}}{dt} = k_{\pm 2}C_{\pm} + k_{\mp 3}C_{\mp} - k_{\pm 1}E_{\pm}X^{\pm}; \qquad \frac{dC_{\pm}}{dt} = k_{\pm 1}E_{\pm}X^{\pm} - (k_{\pm 2} + k_{\pm 3})C_{\pm}; \\ &\frac{dE_{\pm}}{dt} = (k_{\pm 2} + k_{\pm 3})C_{\pm} - k_{\pm 1}E_{\pm}X^{\pm} - \frac{(1 \pm 1)}{2}\frac{dN}{dt}; \quad \frac{dN}{dt} = (k_{-21}N + k_{-22})E_{+} - (k_{21}N + k_{22})N; \end{aligned} \qquad \textbf{[S5]}$$

where we used $X/X^{*} \equiv X^{+/-}$ for notational convenience.

For the parameter set considered, this system has a unique positive fixed point at $X = 1766.1,\ C_{+} = 21.719,\ E_{+} = 6.149,\ N = 2.213,\ E_{-} = 6.562,\ C_{-} = 43.438$ and $X^{*} = 168.79$, which is also a stable node. It further does not exhibit any significant deviations from the deterministic behavior solely due to the internal noise in cycle reactions (Expression **7**) (Fig. 7).

Thus, we can elucidate analytically and verify numerically (data not shown) that the deterministic analysis of this system dynamics predicts some form of exponential decay toward the steady state, as would be expected classically.

II. Stochastic Description

Without loss of generality we apply the noise to the forward enzyme concentration (see Fig. 1) in a way that does not alter the basal level of the enzyme (preserving its average concentration but not the enzyme-complex mass-conservation constraints given earlier) under the stationary density, so that results could be compared against the deterministic predictions. These conditions impose a stability constraint on the driver process and turn the deterministic Eqs. **S2** into

$$\begin{aligned} E_{+}(t) + C_{+}(t) &= E_{+}^{T}(t) = E_{+} + N_{t}, \\ E_{-}(t) + C_{-}(t) &= E_{-}^{T}(t) = E_{-} = Const, \end{aligned} \qquad \textbf{[S6]}$$

where E_{+} is the constant basal enzyme concentration level and N_t is a zero-mean noise process, which describes the nature of the perturbations relevant to the particular system. As discussed earlier, this noise in the activity of the forward enzyme could be due to the

stochasticity in its synthesis and degradation, physical fluctuations in temperature, pH, ligand binding, etc., or may be an appropriate representation of the suitably complex dynamics of the enzyme or its precursor activities propagated from the upstream pathways or systems within the organism. (Note that in the interests of clarity we are considering the internal noise in the cycle mechanism itself to be insignificant in comparison to the external one. This is a reasonable assumption, as was briefly discussed earlier; however, we could have introduced the internal noise into the analytical approach explicitly by, for example, adding another corresponding stochastic term at this point.)

External Noise. Depending on the complexity of the external driver, the total concentration of the forward enzyme, $E_+^T(t)$, could be described in a variety of ways. One simple, yet biochemically meaningful approach is to look at it in terms of the straightforward production–degradation reactions subject to noise, which in a basic differential equation form could be written as

$$dE_+^T(t) = (P - k_d E_+^T(t))dt + \Sigma dB_t, \qquad \textbf{[S7]}$$

where P is the rate of enzyme creation (e.g., by synthesis, activation, vesicle release, etc.), k_d is its effective degradation rate (e.g., proteolysis, inactivation, competitive inhibition, etc.) taken the same for free and complexed forms, and Σ is the fluctuation intensity. This model reflects fundamental cellular dynamics, is consistent with the prior assumptions, and also corresponds to a version of an Ornstein–Uhlenbeck process with a nonzero stationary average $\left\langle E_+^T(t) \right\rangle = P/k_d = E_+$. Note that although a protein-production rate in a cell is often considered to be deterministically constant, it has been repeatedly shown to be a rather noisy process (4-6), thus substantially increasing the potential range of Σ. Then, assuming that the production–degradation and diffusion rates for enzyme concentration are also much faster than the observation time scale, its total stationary concentration can be taken in the "white noise," $\xi(t)$, limit (7-9) as

$$E_+^T(t) = E_+ + \sigma\xi(t), \qquad \textbf{[S8]}$$

where $\sigma = \Sigma/k_d$. That is, this example provides an explicit case of a relatively simple, yet biochemically meaningful mechanism that can serve to generate and impart the external noise on the enzymatic futile cycle in a manner consistent with the general considerations of this work such as those outlined in Eq. **S6**.

Finally, it might be of interest to note here that because the total concentration of the forward enzyme is independent of the cycle dynamics (Expression **7**), its behavior remains the same as described by Eqs. **S7** and **S8** or any similar stand-alone driver whether coupled to the cycle or not. Thus, from the (bio)engineering standpoint, the behavior of the cycle could then be viewed as a noninterfering sensor not only of the stationary levels but of the temporal evolution of the total stochastic enzyme concentration as well.

Stochastic MM Model. As noted earlier, deterministic dynamics of the enzymes comprising the futile cycle is typically considered in MM limit (Eqs. **S1**–**S4**). We now look at the effects of applying the noise driver described in the previous section to one of the futile cycle enzymes and outline the conditions whereby its dynamics could still be considered within MM context, augmented by the appropriate stochastic effector.

In the limit of cycle reaction rates that are significantly faster than those of the noise-generating process (such as that described above) and in the absence of internal noise, futile cycle dynamics becomes deterministic conditional on the total concentration of the forward enzyme. That is, if

$$\Pr\{E_+^T(t) \geq X_0 + K_+\} << 1, \qquad \textbf{[S9]}$$

the MM limit for substrate/product drift (Eqs. **S3** and **S4**) will still hold in probability, thus replacing the classical deterministic criterion given earlier. For drivers of the type given in Eqs. **S7** and **S8**, this condition could be validated explicitly, because their probability density is found analytically. Specifically, Ornstein–Uhlenbeck process stationary probability density is normal with $\mathrm{Var}[E_+^T(t \to \infty)] = \Sigma^2 / 2k_d$ (9), thus the validity criterion for the stochastic MM model of the futile cycle could be taken as

$$E_+ + \frac{3\Sigma}{\sqrt{2k_d}} << X_0 + K_+. \qquad \textbf{[S10]}$$

Then, combining Eqs. **S3** and **S4** with Eq. **S8** recasts the problem into Langevin form, yielding a stochastic MM expression for the level of $X^{(*)}$ as

$$dX^* = -dX = \left[\frac{k_+ E_+ X}{K_+ + X} - \frac{k_- E_- X^*}{K_- + X^*}\right]dt + \frac{\sigma k_+ X}{K_+ + X} dB_t. \qquad \textbf{[S11]}$$

Solving for the level of $X^{(*)}$ directly by using Eq. **S11** is difficult, and the answer is rather complex. However, because we are presently most interested in the response curve, R_N, which requires the knowledge of the stationary system properties only, our approach is to start with the associated Fokker–Planck equation for the probability density of X_t. It can be directly written from **S11** as

$$\frac{\partial P(X;t)}{\partial t} = \frac{\partial}{\partial X}\left\{\left(\frac{k_+ E_+ X}{K_+ + X} - \frac{k_- E_- X^*}{K_- + X^*}\right)P(X;t) + \frac{1}{2}\frac{\partial}{\partial X}\left[\left(\frac{\sigma k_+ X}{K_+ + X}\right)^2 P(X;t)\right]\right\}. \qquad \textbf{[S12]}$$

This equation has the stationary limit, $\partial P(X;t)/\partial t \to 0$, solution

$$P_s(X) = \frac{C}{D(X)} \exp\left[\int_X \frac{2A(X')}{D(X')} dX' \right] = \frac{C}{D(X)} \exp\left[-\phi(X) \right], \qquad \textbf{[S13]}$$

where $\phi(X) = -\int_X \frac{2A(X')}{D(X')} dX'$, yielding an explicit form for the stationary probability density of a noisy futile cycle

$$P_s(X) = \widetilde{C} \left(1 + \frac{K_+}{X} \right)^2 \exp\left[-\frac{2}{(\sigma k_+)^2} \left(k_+ E_+ \mathrm{I}_+(X; K_+) - k_- E_- \mathrm{I}_-(X; K_{+/-}, X_0) \right) \right], \qquad \textbf{[S14]}$$

where $\widetilde{C}$ is the normalization constant chosen so that $\int_0^{X_0} P_s(X) dX = 1$ and

$$\mathrm{I}_+(X; K_+) = X + K_+ \ln\left[X / K_+ \right], \qquad \textbf{[S15]}$$

$$\mathrm{I}_-(X; K_+) = X - \frac{K_-(K_+ + K_- + X_0)^2}{(K_- + X_0)^2} \ln\left[\frac{X}{K_- + X_0 - X} \right] + (2K_+ + K_-) \ln\left[\frac{X}{K_+} \right] - \frac{K_+^2 X_0}{K_- + X_0} \frac{1}{X}. \qquad \textbf{[S16]}$$

From Eqs. **S14-S16** we immediately get the expression for the stationary state nullcline,

$$0 = \left. \frac{\partial p_s(X)}{\partial X} \right|_{X_{ss}} = -p_s(X_{ss}) \frac{2}{(\sigma k_+)^2} \left(k_+ E_+ \frac{\partial \mathrm{I}_+(X)}{\partial X} - k_- E_- \frac{\partial \mathrm{I}_-(X)}{\partial X} + \frac{(\sigma k_+)^2 K_+}{X(K_+ + X)} \right)_{X_{ss}} \qquad \textbf{[S17]}$$

or, equivalently, the response curve (Eq. **3**).

Eq. **3** provides an expression for the level of response $X_{ss}^{(*)}$ in terms of the other parameters of the system. Because this is a quartic polynomial in *X*, we can write down its general analytical solution $X_{ss}^* = X_{ss}^*(k_{+/-}, K_{+/-}, \sigma, E_{+/-})$, but the expression is unwieldy and its meaning is opaque. However, it tells us that at most four real roots are possible, and thus at most two would be stable. That is, in our formulation, stochastic description of the system allows for the potentially bistable behavior, whereby the monostable classical response is split into two stable stationary states through noise-induced bifurcation of the cycle. As we further demonstrate in this work, this analytically predicted bimodality of the stationary distribution is manifested by means of the dynamically bistable behavior of individual system trajectories in the concentration space. In particular, for a set level of $E_+ = \left\langle E_+^T(t) \right\rangle_{t \to \infty}$, the concentration of the cycle substrate/product flip-flops between the two stable states with finite average transition time in a stochastic oscillatory manner under appropriate noise, thus introducing at least two new information channels to the functional repertoire of this mechanism: amplitude and frequency modulation.

It might be of interest to note that the same results could be alternatively obtained by considering the down-going roots of the function

$$\alpha(X) = A(X) - \tfrac{1}{2} D'(X) \qquad \textbf{[S18]}$$

as discussed in ref. 9. The relevant conclusion that could be drawn immediately from this approach is that if the noise on X is additive, i.e., $D(X) = D$ (a frequently considered simple noise model in many applications), then it affects neither the number nor the location of system stationary states. However, if the noise is multiplicative, i.e., $D(X) \neq Const.$, both properties could be changed and other effects ensue. In addition to further highlighting that the previously described effects have nothing to do with ZOU, this framework helps show how noise-induced phenomena could, among other things, be made easier to recognize and its potential effects be accounted for, particularly when considered within the context of (bio)chemical applications.

The results in Eqs. **S14-S16** may now be used further to explicitly calculate the full stationary probability density for the futile cycle system (within the limits our analytical framework) with a given parameter set and, as such, its other properties, including first-passage time moments and oscillation frequency as outlined earlier. For example, Fig. 9 shows the plot of the probability density of X^* for a sample system.

Stochastic Amplification. A noisy enzymatic driver imparts stochastic amplification properties on the product concentration that are quite apart from its deterministic function. To see this, simply note from the deterministic response curve, Eq. **1**, that $E_+^d(X_{ss}^*)$ is a monotonically increasing function (see Fig. 6). In the noisy case, a positive diffusion term, Δ, is further subtracted from the deterministic response, Eq. **3**: $E_+^N(X_{ss}) = E_+^d(X_{ss}) - \Delta(X_{ss})$. Thus, for some chosen level of enzyme driver, e_+, the deterministic signal, X_{ss}^{*d}, satisfies $e_+ = E_+^d(X_{ss}^{*d})$, while the noisy signal, X_{ss}^{*N}, with the same basal enzyme input yields $e_+ = E_+^d(X_{ss}^{*N}) - \Delta(X_{ss}^{*N})$. Comparing the two cases, we see that $E_+^d(X_{ss}^{*N}) > E_+^d(X_{ss}^{*d})$, i.e., because the function is monotonically increasing, $X_{ss}^{*N} > X_{ss}^{*d}$, which confirms stochastic amplification.

As noted earlier, amplification properties of a mechanism are typically quantified as gain (Eq. **4**). Scaling by $\sqrt{k_d/2}$, the futile cycle gain in the limit of small external noise signal amplitudes $\sigma(E_+) \to 0$ becomes

$$G_L\left(X_{ss}(E_+); \sigma(E_+) \to 0\right) \to 20\log_{10}\left[\frac{\sigma(E_+)}{(K_+ + X_{ss})} \times \left|\frac{k_+^2 K_+ X_{ss}(K_- + X_0 - X_{ss})}{k_+ E_+ (K_+ + X_{ss})(K_+ - 3X_0 + 4X_{ss}) + k_- E_-\left((K_- + X_0 - 2X_{ss})(K_+ + 3X_{ss}) + 2X_{ss}^2\right)}\right|\right], \qquad \textbf{[S19]}$$

and in the limit of large external noise $\sigma(E_+) \to \infty$, it is simply

$$G_H\left(X_{ss}(E_+);\sigma(E_+)\to\infty\right)\to 20\log_{10}\left[\frac{X_{ss}}{\sigma(E_+)}\right], \qquad \textbf{[S20]}$$

where $X_{ss} = X_{ss}(E_+) = X_{ss}(E_+;\sigma=0)$. An example of analytical predictions of stochastic gain induced in the cycle mechanism vs. numerical calculations is shown in Fig. 8.

Note that this effect should not be confused with that of stochastic resonance (10), a phenomena long known to occur in various biological organisms (11, 12), which has a resonant frequency and requires in its basic definition a weak oscillatory baseline signal to be present, thus limiting the relevance of the effect only to those systems in which such conditions are present. No such requirement exists for the effect discussed herein.

Stochastic Signaling. As has been noted, analytically quantifying frequency-domain behavior of system oscillations is, in general, significantly more difficult than its amplitude, because the former is determined by the overall shape of the probability distribution of the process, whereas the latter substantially depends only on the position of its stationary states. A basic measure of such behavior is oscillation period, which in this case is itself a stochastic quantity. To derive an analytical expression for the first moment of the oscillation period (Eq. **5**), we decompose it into forward and backward transition time moments,

$$\begin{aligned}\left\langle T(X_{ss}^1 \rightleftarrows X_{ss}^2)\right\rangle &= \left\langle T(X_{ss}^1 \to X_{ss}^2) + T(X_{ss}^1 \leftarrow X_{ss}^2)\right\rangle \\ &= \left\langle T(X_{ss}^1 \to X_{ss}^2)\right\rangle + \left\langle T(X_{ss}^2 \to X_{ss}^1)\right\rangle,\end{aligned} \qquad \textbf{[S21]}$$

that for a one-dimensional bistable system could be written explicitly (9, 13) as

$$\begin{aligned}\left\langle T(X_{ss}^1 \to X_{ss}^2)\right\rangle &= \int_{X_{ss}^1}^{X_{ss}^2} \frac{2dX}{D(X)P_s(X)} \int_{-\infty}^{X} dX' P_s(X'), \\ \left\langle T(X_{ss}^2 \to X_{ss}^1)\right\rangle &= \int_{X_{ss}^1}^{X_{ss}^2} \frac{2dX}{D(X)P_s(X)} \int_{X}^{\infty} dX' P_s(X'),\end{aligned} \qquad \textbf{[S22]}$$

where $X_{ss}^1 < X_{ss}^2$. Combining Eqs. **S21** and **S22** we then obtain the equality in Eq. **5**.

To obtain the asymptotic expansion of the equality in Eq. **5** we first substitute Eq. **S13** in

$$\left\langle T(X_{ss}^1 \rightleftarrows X_{ss}^2)\right\rangle = \frac{2}{C}\int_{X_{ss}^1}^{X_{ss}^2} dX \exp\left[\int_X dX' \frac{2A(X')}{D(X')}\right] = \frac{2}{C}\int_{X_{ss}^1}^{X_{ss}^2} dX \exp\left[\phi(X)\right]. \qquad \textbf{[S23]}$$

For a bistable distribution, the integrand in Eq. **S23** has a single maximum at the saddle point, X_{sp}. As a Laplace integral, it can now be expanded asymptotically (14) in the small noise limit, $\sigma \to 0$, as

$$\int_{X_{ss}^1}^{X_{ss}^2} dX \exp[\phi(X)] \sim \frac{\sqrt{2\pi}\exp[\phi(X_{sp})]}{\sqrt{-\phi''(X_{sp})}} = \frac{\sqrt{2\pi}}{\sqrt{-\phi''(X_{sp})}} \frac{C}{D(X_{sp})P(X_{sp})}. \qquad \textbf{[S24]}$$

Substituting **S24** into **S23** yields Eq. **5** for the average oscillation period

$$\langle T(X_{ss}^1 \rightleftharpoons X_{ss}^2) \rangle \sim \frac{\sqrt{8\pi}}{D(X_{sp})P(X_{sp})\sqrt{-\phi''(X_{sp})}}. \qquad \textbf{[S25]}$$

Because Eq. **S25** implicitly depends on the normalization constant, C, which does not have an explicit analytical expression, it might be of interest to note that an expression for average period that is independent of C can be provided. Because a bistable distribution integrand in Eq. **S13** has double maxima at the stationary states, $X_{ss}^{1,2}$, its asymptotic expansion is

$$\frac{1}{C} = \int_{-\infty}^{\infty} \frac{dX}{D(X)} \exp[-\phi(X)] \sim \sum_{n=1,2} \frac{\sqrt{2\pi}}{\sqrt{\phi''(X_{ss}^n)}} \frac{e^{-\phi(X_{ss}^n)}}{D(X_{ss}^n)}. \qquad \textbf{[S26]}$$

Combining **S23**-**S26** gives an explicit analytical expression

$$\langle T(X_{ss}^1 \rightleftharpoons X_{ss}^2) \rangle = \frac{2}{C} \int_{X_{ss}^1}^{X_{ss}^2} dX \exp[\phi(X)] \sim \sum_{n=1,2} \frac{4\pi e^{\phi(X_{sp})-\phi(X_{ss}^n)}}{D(X_{ss}^n)\sqrt{\phi''(X_{ss}^n)}\sqrt{-\phi''(X_{sp})}} \qquad \textbf{[S27]}$$

that is independent of *C*, asymptotic in the same limit, $\sigma \to 0$.

Relationship to ZOU. In the classical deterministic limit, behavior of the enzymatic cycle mechanism has been studied extensively within the ZOU context noted earlier (15-17). Although many aspects of this treatment are still applicable in the stochastic case, the effects discussed earlier (notably the stochastic amplification and signaling) are fundamentally different from ZOU in both their nature and origin, because they are solely induced and can be substantially regulated by noise. Specifically, observing a sharp sigmoidal response of the deterministic futile cycle switch shown in Fig. 6 may lead one to assume naively that if the system were close enough to the transition region, bistability might simply be induced by the E_+ "noise envelope" spreading to the opposite side of the switch. This is a fundamentally inappropriate way of looking at an individual mechanism not only because the ZOU description is not applicable to systems with low molecular count (18) but also because using it within such an analysis would assume that

the shape of the response curve shown in Fig. 6 remains the same when transitioning from the deterministic to the stochastic treatment, which is manifestly incorrect, as can be seen by comparing Eqs. **1** and **3**. In fact, because $R_N(X_{ss}^{(*)}, E_+; E_-) = 0$ represents a relationship between stationary-state levels of the enzyme and substrate/product, we should expect, in general, to get a different relationship for different types of the external noise driver, thus rendering the aforementioned logic further invalid. To put this in different terms, for each different system master equation that incorporates an external noise as a set of additional reactions and thus defines a different joint probability solution, a different relationship between $X_{ss}^{(*)}$ and E_+ would arise. That is, noise acts as an operator, altering the form of the response relationship, $R_N = N[R_0]$, and, potentially, the dynamic behavior of the system relative to its unperturbed state as shown in Eq. **3**. In particular, this means that noise regulation may offer new methods of control over this mechanism or, conversely, be helpful in inferring the structure of the larger networks in which these systems are embedded (as is discussed further in the article).

III. Additional Citations

a. *In situ* biochemical systems with enzymatic cycles (19-26)
b. Nonlinear stochastic effects (27-31)
c. Stochastic effects in biomolecular systems (32-36), including metabolism (37, 38) as well as signal transduction and gene expression (39-41)
d. Enzymatic futile cycles in:
    i. GTPase cycles (42)
    ii. Mitogen-activated protein cascades (43-45)
    iii. Glucose mobilization (46)
    iv. Cell division/apoptosis (47)
    v. Checkpoint control (48)
    vi. Actin treadmilling (49)
    vii. Metabolism (50)
    viii. Two-component systems and phosphorelays (51-53)
e. Chaotic process in cardiac or neural tissue (54, 55)
f. Multiplexing in calcium spiking (56-60)
g. Using noise filtering for (bio)chemical system structure inference (61-63)
h. Chemical master equation (64-67)
i. Filtering and shaping of oscillatory signals by biological systems (68-72)

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