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Thank you for your email on September 24th, 2014, inviting us to submit a revised version of our manuscript, "Amplitude metrics for cellular circadian bioluminescence reporters" (MS: 2014BIOPHYSJ304278R) by Peter C. St. John, Stephanie R. Taylor, John H. Abel, and Francis J. Doyle III.

We thank the reviewers for their second round of comments of the manuscript, in particular Reviewer #2 for their continued attention to detail. We believe addressing these remaining concerns and suggestions have improved the polish of the manuscript.

Please see our detailed responses to the reviewers below:

Reviewer #1

The authors have largely responded you my concerns.

Typos and suggestions

- p. 2: "fail to capture the collective dynamics of a population oscillators"

This typo has been addressed, the sentence now reads:

> **Page 2**
>
> Ordinary differential equation (ODE) models of gene regulation are capable of describing the amplitude and phase-resetting behavior of single cells, but fail to capture the collective dynamics of a population **of** oscillators.

- mu is defined a few lines after it is first used in Eq. (20). Perhaps define it first?

This change has also been made.

> **Page 7**
>
> To define an amplitude change metric for such a case, we compare a perturbed trajectory $x(t)$ to a phase-shifted limit cycle reference $y(t)$,

for which $x(t) \to y(t)$ for sufficiently long times. Since $x(t)$ approaches the reference as $t \to \infty$, **the means of both trajectories are equal and can be calculated by**

$$\mu := \int_0^{2\pi} \frac{x^\gamma(\theta)}{2\pi}\, d\theta. \tag{20}$$

The amplitude change metric is defined as

$$\begin{aligned} \Delta A(x(t), y(t)) &:= \int_0^\infty (x(t)-\mu)^2 - (y(t)-\mu)^2\, dt \\ &= \int_0^\infty h(t)\, dt. \end{aligned} \tag{21}$$