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C·T·S·B CONTROL THEORY & SYSTEMS BIOLOGY

Engineering Sensor-Based Antithetic Integral Controllers for Enhanced Dynamic Performance & Noise Attenuation

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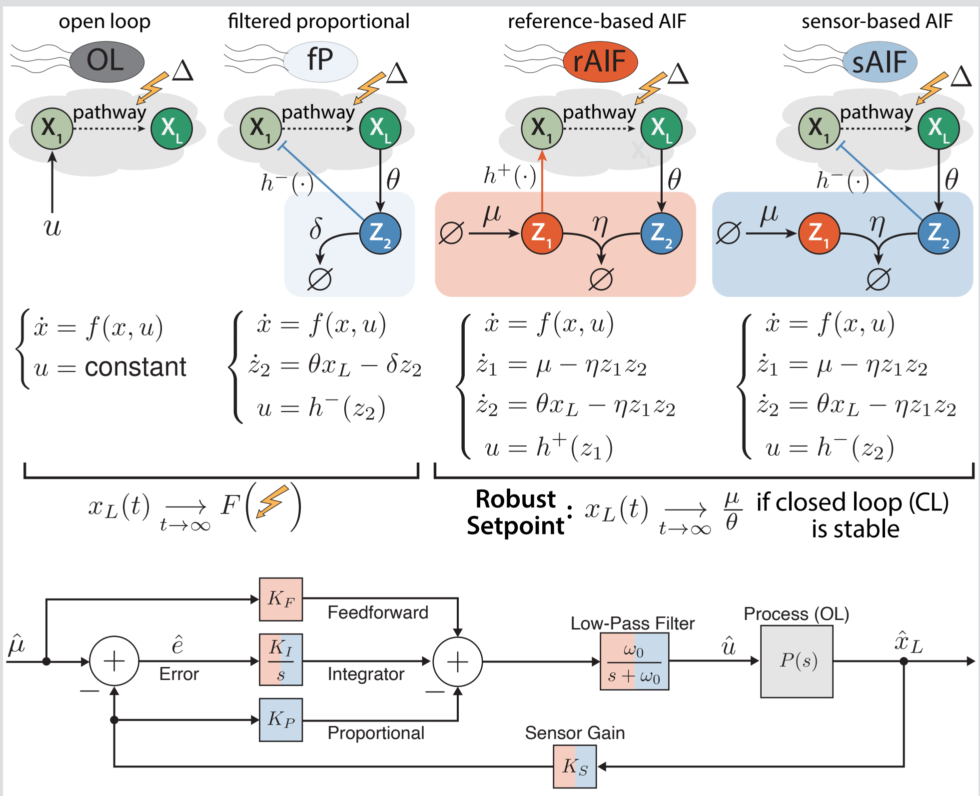
Living cells naturally use feedback to maintain homeostasis. Synthetic biology aims to harness this principle to build circuits that can automatically correct their behavior under disturbances [1]. A key goal is **robust perfect adaptation (RPA)** — the ability to return to a setpoint despite changes or noise. The **reference-based antithetic integral feedback (rAIF)** motif [2] achieves this but may sacrifice speed and increases variability. We show that a **sensor-based** version of the **AIF (sAIF)** introduces extra proportional feedback by simply modifying the actuation mechanism and without additional circuitry [3]. We establish theoretically and experimentally in bacteria (using inteins) that sAIF preserves RPA while simultaneously enhancing dynamic performance and attenuating noise.

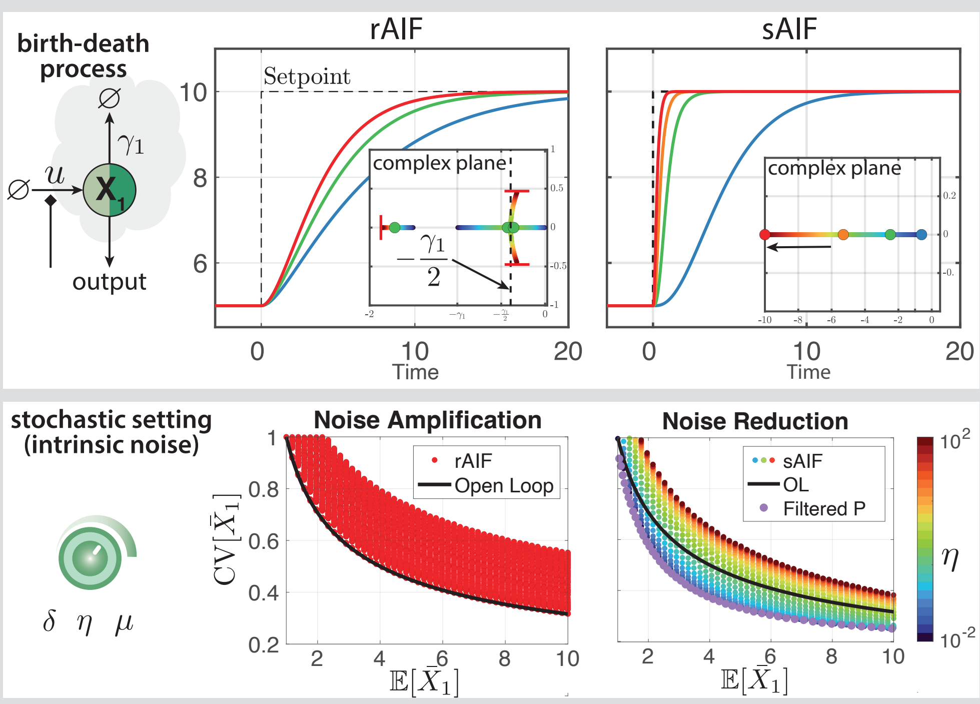
1. Concept & Design of Chemical Reaction Networks



- Both rAIF and sAIF achieve RPA
- Linear perturbation analysis reveals:

rAIF = integral + feedforward sAIF = proportional + integral (PI)

2. Theoretical & Computational Results



- **Deterministic analysis:** Root locus results show that rAIF cannot shift 2 eigenvalues arbitrarily left, limiting speed. This constraint is removed in sAIF, allowing full pole placement and faster, well-damped dynamics.
- **Stochastic analysis:** Linear noise approximation indicates that sAIF can reduce output noise (CV) below open-loop levels, but its improvement is bounded by the P controller if δ can be tuned. This confirms that sAIF's noise attenuation arises from its „hidden" proportional component.

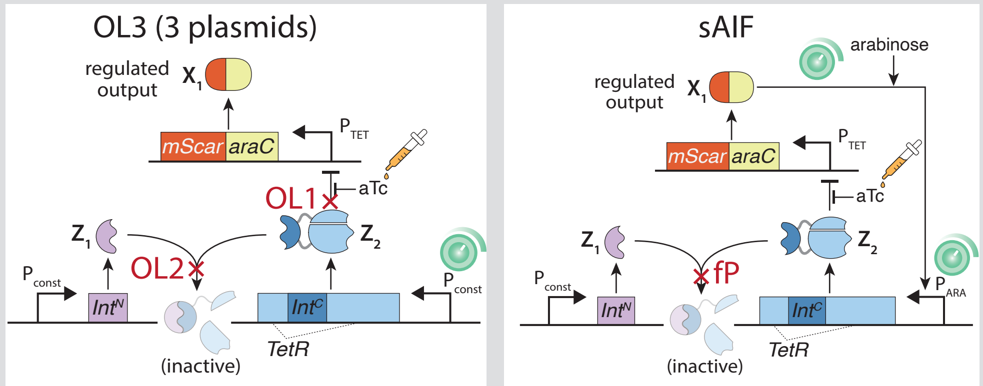
Non-ideal Setting: Dilution of control species $Z_1 \xrightarrow{\delta} \emptyset$ as cells grow limits RPA to near-RPA. So why add extra circuitry of sAIF, and not just stick to fP?

Theorem: *Given a fixed repressor* Z_2 *and a desired setpoint we have:*

$$\lim_{t\to\infty}\left|\frac{\partial x_L(t)}{\partial \Delta}\right|^{\text{sAIF}} < \lim_{t\to\infty}\left|\frac{\partial x_L(t)}{\partial \Delta}\right|^{\text{fP}} \quad \text{and} \quad \lim_{t\to\infty}\frac{\partial}{\partial \eta}\left|\frac{\partial x_L}{\partial \Delta}\right|^{\text{sAIF}} < 0 \quad \forall \text{monotonic OL}$$

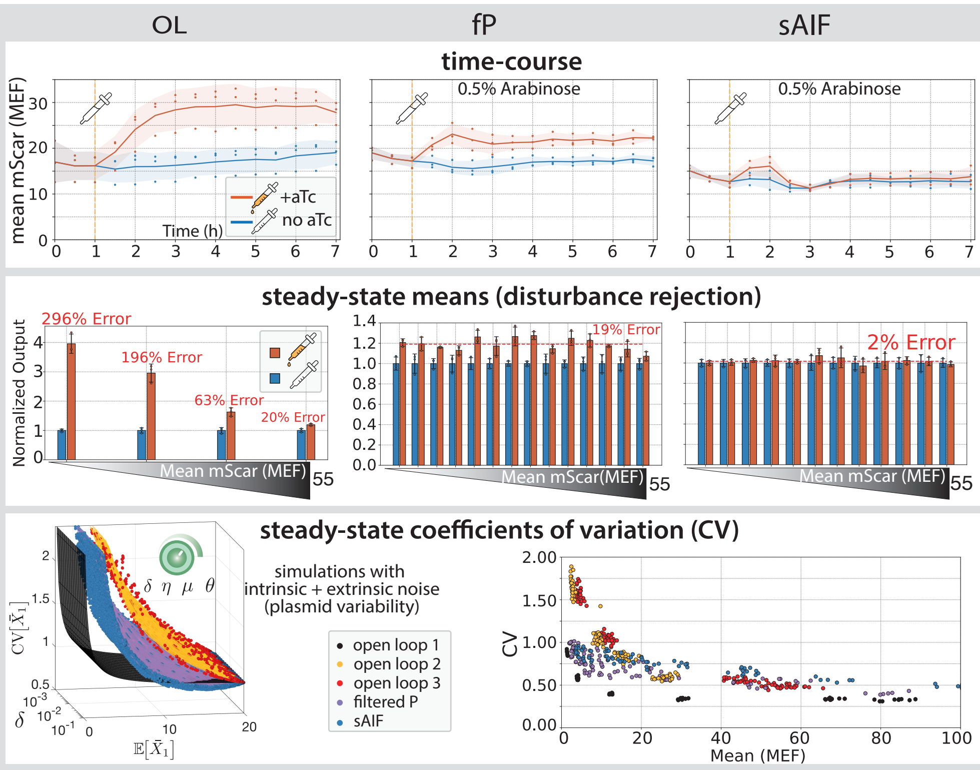
3. Genetic Implementation in Bacteria with Split Inteins

- Split inteins are small proteins that can undergo splicing reactions.



- 3 open loops: OL1, OL2, and OL3 with 1, 2 and 3 plasmids, respectively.
- 2 closed loops: fP and sAIF.
- Regulated process: gene expression.

4. Experimental Results



- sAIF enjoys disturbance rejection over a wide dynamic range, delivers high dynamic performance, and attenuates noise compared to OL2 & OL3

References

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2. Briat, C., Gupta, A., & Khammash, M. (2016). Antithetic integral feedback ensures robust perfect adaptation in noisy biomolecular networks. Cell systems, 2(1), 15-26.
3. Filo, M., Hou, M., & Khammash, M. (2023). A hidden proportional feedback mechanism underlies enhanced dynamic performance and noise rejection in sensor-based antithetic integral control. bioRxiv, (under revision in Cell Systems).

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