Single and Multi-Objective *in Silico* Evolution of Tunable Genetic Oscillators

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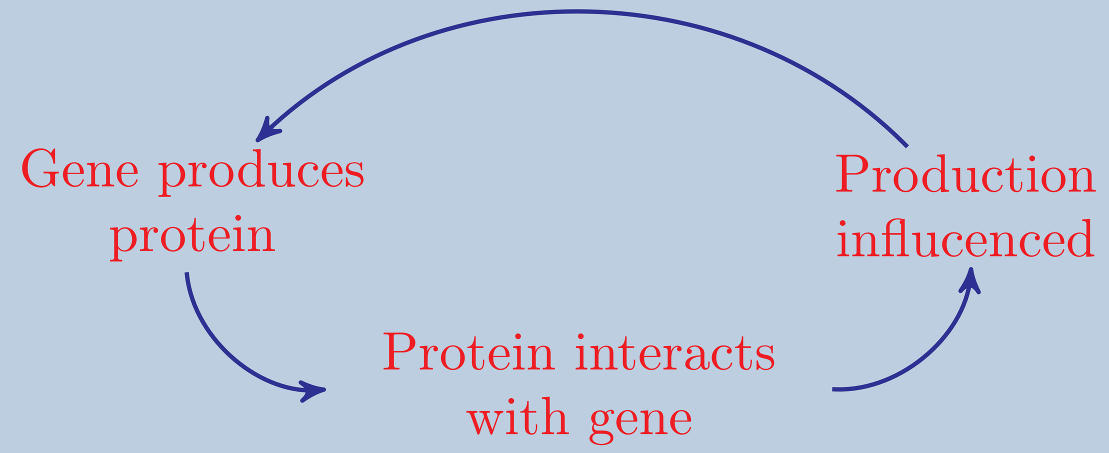
1) Introduction

Computational modelling and analysis of biological network motifs are essential for understanding of biological systems. Genetic oscillators, which can be modelled by ordinary differential equations (ODEs), are an important motif in gene regulation and observed in many biological systems. Here, we investigate the influence of fitness setup on the synthesis of a genetic oscillator. The production of oscillations is important in biological systems [1, 2] and the ability to accurately tune the period of a genetic oscillator is vital in biological modelling.

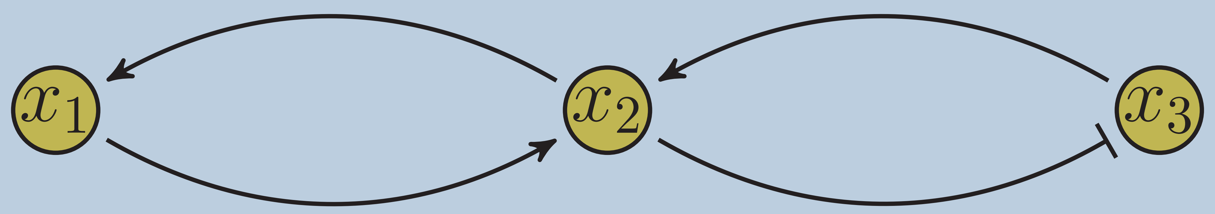
Biological Event	Time Scale	REF
cardiac rhythms	seconds	[3]
mitosis cell cycles	minutes	[4]
sleep/wake cycle	hours	[5]
circadian rhythm	days	[6]
ovarian cycle	weeks	[3]
predator-prey populations	years	[7]

2) Gene Regulatory Networks

GRNs are groups of genes that interact with each other via their protein production.



The following GRN is able to produce a sustained oscillation,



and is modelled using the following ODEs;

$$\dot{x}_1 = a_{12}H^a_{12}(x_2) - a_{11}x_1 \quad (1)$$

$$\dot{x}_2 = a_{23}\frac{1}{2}\Big(H^a_{21}(x_1) + H^a_{23}(x_3)\Big) - a_{22}x_2 \quad (2)$$

$$\dot{x}_3 = a_{32}H^r_{32}(x_2) - a_{33}x_3 \quad (3)$$

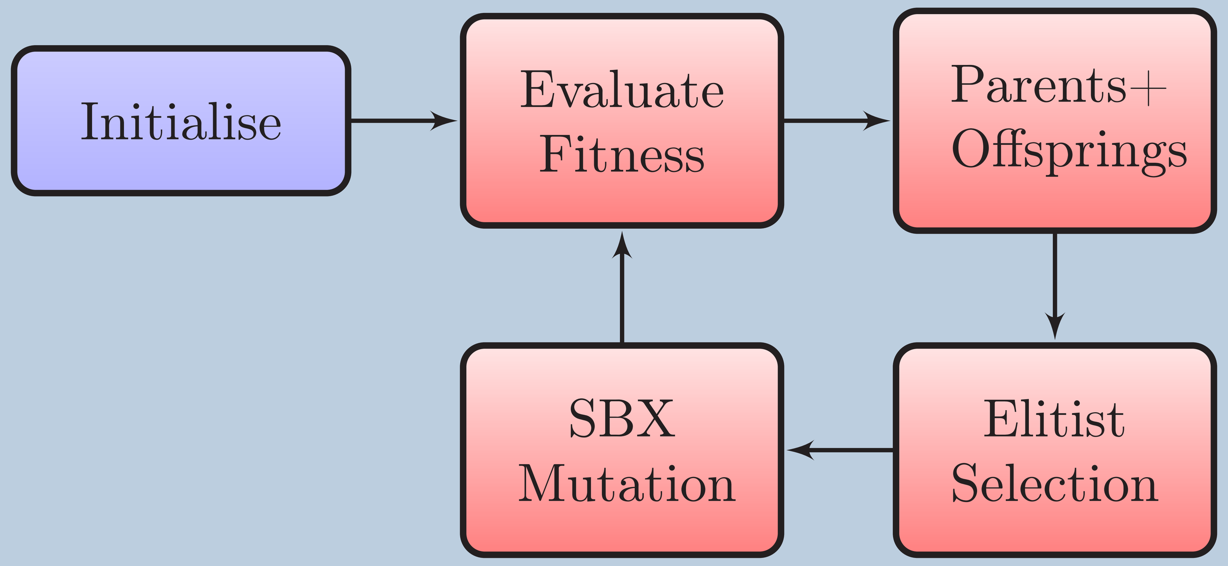
The interaction between two genes is modelled using Hill functions and combined using summation logic;

$$H^a_{ij}(x_j) = \frac{\beta x_j^n}{\theta_i^n + x_j^n}\ ;\ H^r_{ij}(x_j) = \frac{\beta}{1 + (x_j/\theta_i)^n} \quad (4)$$

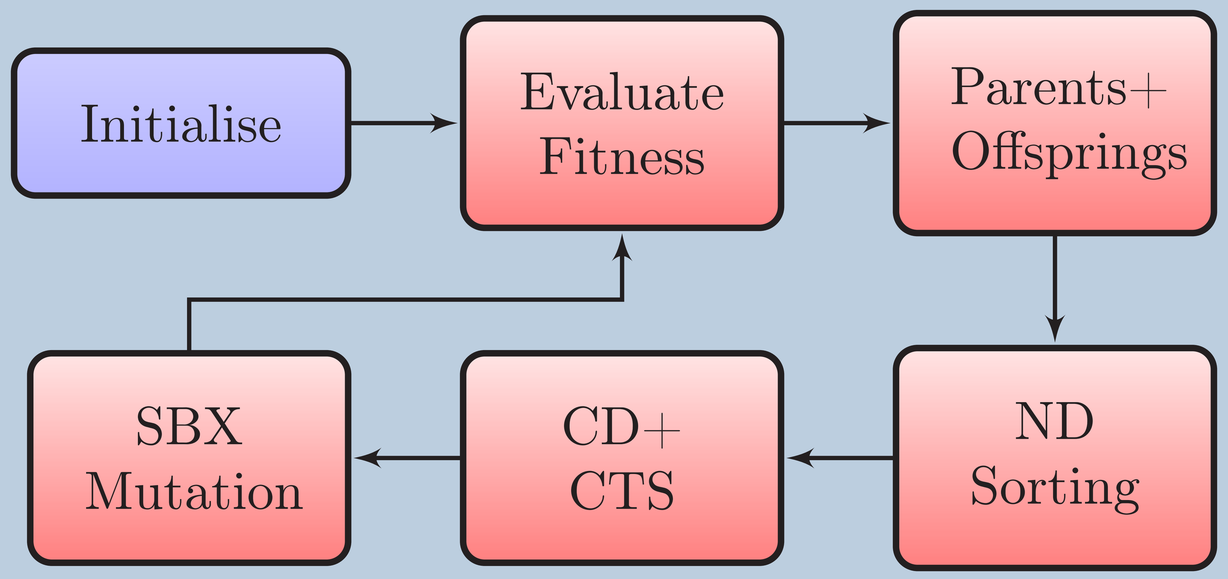
3) Evolutionary Algorithms

Here we use NSGA-II [9] with Simulated Binary Crossover and Polynomial Mutation operations [10] to optimise the system parameters.

Single Objective (SO)



Multi-Objective (MO)



Evolutionary algorithm parameters

Population Size	Generations	Simulations
100	100	50

4) Single Objective Setup

Time Domain

A self sustained oscillation is producible by reducing the error between the GRN dynamics and a desired state described by a sine wave.

$$x^d_{tg}(t) = \sin\left(\frac{2\pi t}{T}\right) \quad (5)$$

We define a fitness function as the mean squared error (MSE) between the GRN and the desired state

$$f(t_s) = \frac{1}{R}\sum_{r=1}^{R}\sum_{t=0}^{N}\Big(x^i_{tg}(r,t) - x^d_{tg}(t)\Big)^2 \quad (6)$$

Frequency Domain

We also investigate a frequency based desired state by calculating the maximum value of the Fourier Transform [8] of the desired sine wave.

$$\omega^d_{tg} = MAX\left\{\hat{F}\left[\sin\left(\frac{2\pi t}{T}\right)\right]\right\} \quad (7)$$

We define a similar MSE fitness function to the time domain between the desired state, ω^d_{tg}, and the Fourier Transform of the state of the GRN, $x^i_{tg}(r,t)$.

$$f(\omega_s) = \frac{1}{R}\sum_{r=1}^{R}\sum_{t=0}^{N}\Big(\hat{F}\left[x^i_{tg}(r,t)\right] - \omega^d_{tg}\Big)^2 \quad (8)$$

5) Multi-objective Setup

Specified Frequency

Here we use a mutli-objective setup with the time and frequency domain objectives (Eq. (6) and Eq. (8)) from the single objective setups together.

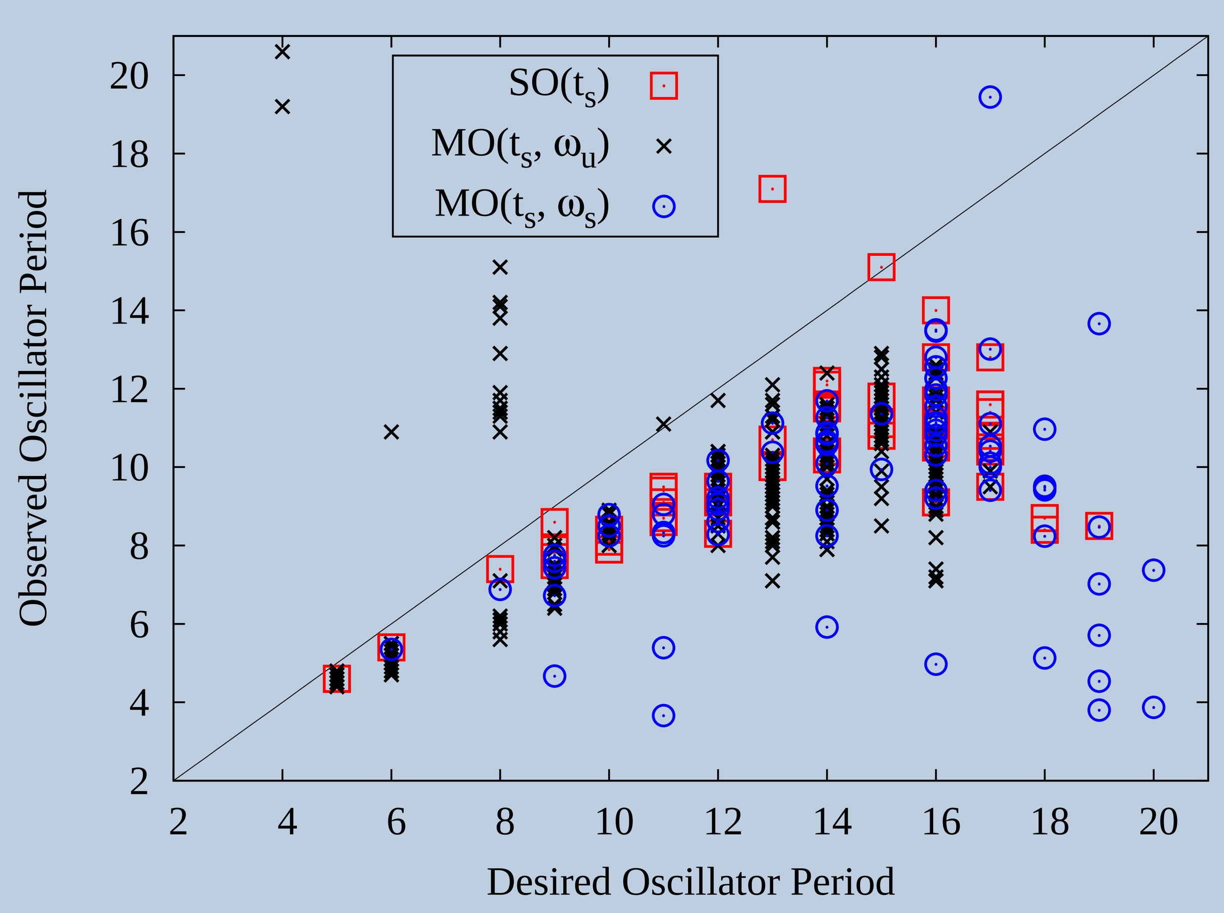
Unspecified Frequency

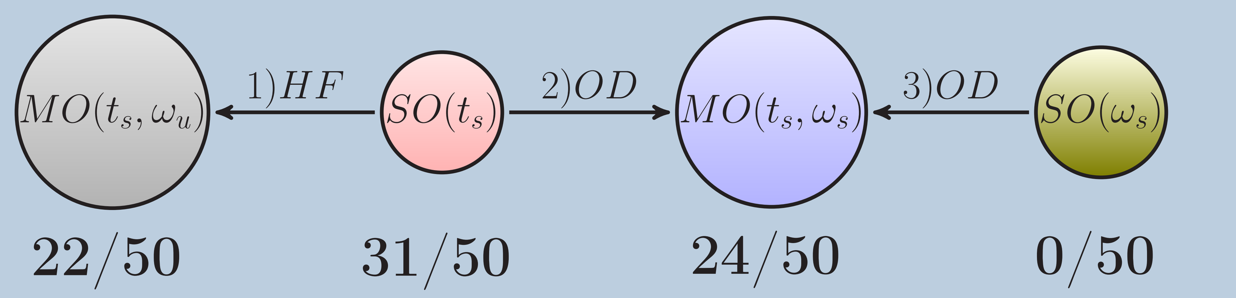
We use the time domain objective (Eq. (6)) with a frequency domain objective that does not specify the oscillator characteristics.

$$f(\omega_u) = \frac{1}{R}\sum_{r=1}^{R}\frac{1}{MAX\{\hat{g}(r,\omega)\}}\int \hat{g}(r,\omega)\ d\omega \quad (9)$$

$$\hat{g}(r,\omega) = \hat{F}\left[x^i_{tg}(r,t)\right] \quad \text{(FT of GRN).} \quad (10)$$

6) Results, Conclusions and Future Work





Conclusions

- MOV may depend on $f(\ )$ setup and domain
- Additional $f(\omega)$ do not aid tunabillity overall
- NSGA-II + $f(\omega)$ unable to produce oscillations

Future Work

- Further investigation into $f(\omega)$
- Compare NSGA-II to evolution strategy
- Auto regulation loops to aid tunabillity [11]

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