Coupling hair follicle cycles to produce oscillating patterns

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Introduction

Synchronous oscillations in biological systems are inevitable yet enigmatic occurrences. Throughout the body, millions of individual cells are able to communicate and produce large-scale signals that produce brain waves and heart beats. Coat patterns arise spontaneously on the skin of many animals due to local organization of skin cells. All of these large-scale processes are the result of the synchronization of millions of small-scale cycles (Maini).

One of the many elusive biological clocks is the hair follicle. A fixed number of follicles, determined early in life, cycle regeneratively through phases of growth, apoptosis, and rest. Once the follicle has formed through morphogenesis, it begins the hair cycle with the apoptotic state, catagen. This phase is followed by a period of relative rest called telogen. The growth phase, known as anagen, involves the creation of a new hair shaft from the mesenchyme (Muller-Rover *et al*).

It is important to note that each follicle is an independent entity and will retain its properties even in the event of transplantation. It cycles autonomously with a certain period that is fixed from its morphogenesis and depends on its location on the body. In humans and pigs, the follicular phases are staggered so that there is no seasonal shedding and growing period (Stenn and Paus). Although the cycling machinery is completely contained within the follicle and can function autonomously, external signals can alter the duration and character of various phases within the cycle (Paus and Foitzik). Some

animals, including certain rodents, display large-scale synchronization of the follicular cycle. Especially in younger individuals, patches of hair cycle together in waves across the animal's body.

Of particular interest in the study of hair cycling are nude mice. The skin in the immediate vicinity of the follicle changes color depending on the current phase of the hair cycle. Since these mice are hairless, it is possible to observe hair cycle patterns on the integument (Asai *et al.*) One such mutant strain, the $Foxn^{tw}$, is unable to sustain hair growth once the melanocytes begin to accumulate in the follicle, and so the hair falls out at the beginning of anagen. Pigment appears to originate in the armpits and move in waves across the entire body in a pattern that reflects the large-scale synchronization of the individual follicular cycles (Suzuki *et al*).

With the $Foxn^{tw}$ mice as an inspiration, the objective of this study is to develop a model for the communication and resulting synchronization of hair follicles.

Materials and Methods

The derivation of a mathematical model is complicated by the fact that the exact molecular basis of hair follicle cycling remains unknown. However, it has been suggested that the follicle cycle is correlated with the cell cycle of the dermal fibroblasts. Both oscillate autonomously, regardless of seasonal changes, but are sensitive to external stimuli (Paus and Foitzik). Thus, a common mathematical model of the cell cycle will be used as a basis for the follicular cycle.

There are two major requirements for biochemical oscillators. The first is that they must involve at least two variables, which in this case is assumed to be an activator

and an inhibitor. The second requirement is that at least one of the chemicals must be autocatalytic. One common biological model which exhibits oscillations involves an autocatalytic activator and an inhibitor, both of which have a production source and are subject to decay (Fall *et al*).

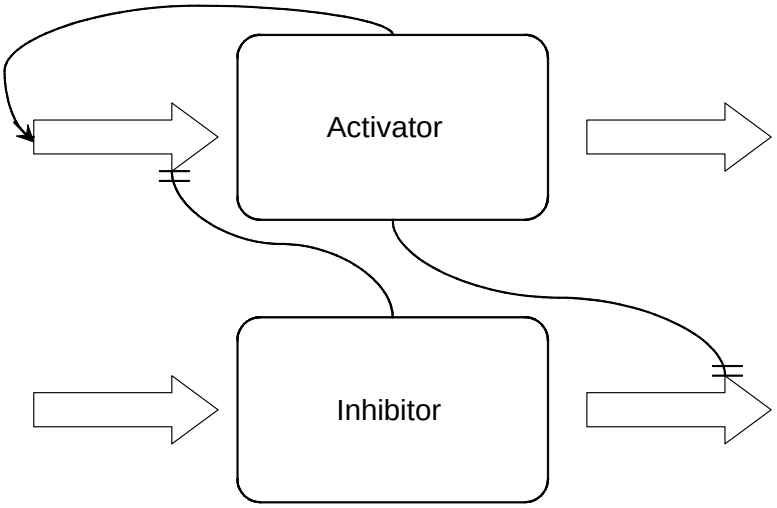

Figure 1: Common model of an activator/inhibitor biochemical oscillator (modified from Fall *et al*).

$$\frac{dx}{dt} = \frac{\varepsilon^2 + x^2}{1 + x^2} \cdot \frac{1}{1 + y} - ax$$

Fall, *et al.*

$$\tau \frac{dy}{dt} = b - \frac{y}{1 + cx^2}$$

In this dimensionless system of equations, *x* represents the activator and *y* represents the inhibitor. Epsilon reflects the extent of autocatalysis, and *a* is a measure of decay. The *c* parameter is proportional to the activator's inhibition of the decay of the inhibitor, and *b* is the production term of the inhibitor. The τ was inserted for simplicity of analysis and essentially substitutes for the decay term of the inhibitor.

Since an analytical solution to these equations is impossible, their long-term behavior will be studied using qualitative analysis. Assuming that the cells communicate

through the diffusion of activators and inhibitors, different modes of coupling will be simulated to determine whether the follicles are synchronized through the activator, inhibitor, or both. An optimal coupling function will be determined which creates traveling waves. Additionally, it will be useful to find a parameter whose variance produces a Hopf bifurcation. This makes it possible to produce a stable limit cycle that is a product of the amount of a certain molecule. Once a limit cycle has been found for specific parameters, the sensitivity of the solution to initial conditions can be evaluated.

Based on the results of this simple model, a complex model that is more specific to the cell cycle will be examined for similar criteria.

$$\frac{dX}{dt} = k_1 - (k_2' + k_2''Y)\,X$$

Fall, *et al.*

$$\frac{dY}{dt} = \frac{(k_3' + k_3''A)(1-Y)}{J_3 + 1 - Y} - \frac{k_4 mXY}{J_4 + Y}$$

Once again, the X represents an activator (cyclin/Cdk dimer) and Y is the inhibitor (Cdh2/APC complex). The k's are rate constants, the J's are Michalis constants, and the constants *A* and *m* represent the concentration of a protein and the mass of the cell, respectively

(Fall *et al*).

Expected Results:

Given the right parameters, the model will ideally produce a stable limit cycle. This limit cycle should be dependent upon the change in one or two crucial parameters, and will hopefully produce oscillations which resemble patterns similar to those observed in animals. The ability to synchronize will depend upon the relative coupling between the activator and the inhibitor.

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