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A condition for regeneration of a cell chain inspired by the Dachsous-Fat system

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Abstract. Regeneration phenomena in cricket legs and Planarians have recently been studied at the single cellular level. Within a cell, Dachsous and Fat molecules, and between cells, Dachsous-Fat heterodimers, are considered related to regeneration phenomena. Inspired by recent studies on Dachsous and Fat, we modeled a cell chain with heterodimers and analyzed it. We parameterized redistribution of heterodimers during cell division, which is poorly understood. We then derived equations in parameters to regenerate the heterodimeric pattern even if part of the cell chain is excised. This excision model contained eight parameters, and hence we used a few algebraic methods to suit models that are described by a set of polynomials. A number of biological phenomena have recently been analyzed through algebraic methods; thereby, we can directly derive equations in parameters. The derived equations show that some specific relation between the redistribution ratio of heterodimers allows a cell chain to regenerate its heterodimeric pattern.

Keywords. Dachsous-Fat system, regeneration, algebraic methods, developmental biology

1. Introduction

Regeneration phenomena have been studied through various models. Taking cockroach leg regeneration for instance, it has been studied through the positional information model [23, 22], the polar coordinate model [9, 10, 6, 7], and the boundary model [15, 16]. The positional information model provided an explanation and estimation of regeneration for cockroach legs by assigning positional values to them. The polar coordinate model was established in two-dimensional space to explain the distal transformation such as supernumerary leg production, where tissues with the same positional value along one axis, but with different values along another axis, are grafted. Interpreting the two-dimensional space as the complex number, Cummings and Prothero modeled the regeneration of cockroach legs and succeeded in explaining the number, place, and handedness of regenerated and added legs using Cauchy's integral theorem [8]. Extending this model to vector fields, Totafurno and Trainor succeeded in explaining both contralateral and ipsilateral regenerations [21]. Meinhardt's boundary model advanced explaining these phenomena by considering limbs and legs to be composed of some blocks [16].

Apart from these theoretical models, recent studies have led to models at the single cellular level [2]. Dachsous-Fat, for example, is considered to facilitate regeneration of cricket legs [3]. The Dachsous-Fat signaling system is also deemed an entity to realize the steepness hypothesis where the leg size and regeneration are regulated through a *gradient* across cells [14]. As studies at the single cellular level have made progress, it has become necessary to propose a unified view of the conventional classification of regeneration: epimorphosis and morphallaxis. Epimorphosis regeneration is expected to start with a blastema that proliferates to restore the missing part, while morphallaxis is thought not to form a blastema, but to rearrange remaining cells to regenerate a smaller whole animal. As an example of unified views, a notion of *distalization* and *intercalation* was proposed [1] that considers regeneration to start with a blastema having the distal positional value, which interacts with original cells to induce intercalary wound healing.

The author had studied regeneration phenomena through numerical simulations of chaotic elements [24], where cell types were regarded as various types of attractors within chemicals' state space, resulting in a unified view of cockroach leg regeneration [25]. The author had also modeled a multicellular organism using a Lindenmayer system to derive a condition for coexistence of various cell types [27], in which symbolic computation was used to analyze the model with parameters. Here we also used symbolic computation to suit analysis of models without substituting concrete values into parameters. We modeled a cell chain with the Dachsous-Fat heterodimers. We then parameterized redistribution ratios of heterodimers during cell division, and calculated equations to allow a heterodimeric pattern to regenerate itself even if its part is excised. The derived equations show that some specific redistribution of heterodimers enables a cell chain to regenerate its heterodimeric form.

Symbolic computation has been developed to manipulate mathematical equations and expressions in symbolic

and exact form instead of in an approximate form during calculation. Recently, symbolic computation has been applied to a number of biological problems [13]. It had worked well with polynomials only, but has extensively dealt with biological models described as a set of differential equations [5].

2. Model

We constructed a cell-chain model inspired by the Dachsous-Fat system, which is considered to play an important role in regeneration [14]. Figure 1A illustrates Dachsous-Fat heterodimers that exist between cells. It has been said that the heterodimer arises from free active Dachsous (Ds) and Fat (Ft) molecules within cells [14]. Ds and Ft molecules is further expected distributed on the cell surface when a cell divides into two, so that Ds-Ft heterodimers become redistributed accordingly. Little is, however, known about the way in which they are redistributed because the metabolism of the Ds-Ft signaling and heterodimers remains obscure [3]. We hence modeled this redistribution and calculated a condition for regeneration. For this purpose, here we parameterized the redistribution of heterodimers during cell division, as illustrated in Fig. 1B. We grant that active Four-jointed (Fj), Ds, and Ft molecules within cells and the interactions among them are as important in regeneration as Ds-Ft heterodimers between cells, but we focused on the distribution of heterodimers as a result of these interactions.

Let l_{ft} and l_{ds} be the amounts of Ft and Ds, respectively, of heterodimers on the left-side surface of the left cell (see Fig. 1B). Likewise, let r_{ft} and r_{ds} be the amounts of Ft and Ds, respectively, of heterodimers on the right-side surface of the right cell. After cell division, the heterodimers are redistributed to the newly created cell wall. Accordingly, let n_{ft} and n_{ds} be the amounts of Ft and Ds, respectively, of heterodimers on the left-side surface of the right cell. We set the redistribution ratio of these values with parameters $x_f, x_d, y_f, y_d, z_f, z_d, u_f$, and u_d as follows:

$$\begin{cases} n_{\mathrm{ft}} = x_f l_{\mathrm{ft}} + y_f l_{\mathrm{ds}} + z_f r_{\mathrm{ft}} + u_f r_{\mathrm{ds}}, \\ n_{\mathrm{ds}} = x_d l_{\mathrm{ft}} + y_d l_{\mathrm{ds}} + z_d r_{\mathrm{ft}} + u_d r_{\mathrm{ds}}. \end{cases} \tag{1}$$

Under this parameterization, we started with a single cell and increase the cell number through division. Notice that the amounts of Ft and Ds of heterodimers on the right-side surface of the left cell (namely, the right side of the newly created wall) are equal to n_{ds} and n_{ft}, respectively, because of the (trans-)heterodimeric form.

2.1. Simulation of Regeneration

We constructed a **regeneration simulation** that consists of a **development** phase and an **extract** phase.

The development phase consists of the following three procedures:

Distalize: We set a fixed pair of values at both ends of a cell chain. We set l_{ft} and l_{ds} of the leftmost cell as a and b, respectively; likewise, we set r_{ft} and r_{ds} of the rightmost cell as c and d, respectively. This procedure stems from the wound healing of Planarians when they are excised [1, Fig. 2]. Stumps of excised Planarians are observed obtaining the most proximal and distal positional values, called "distalization." We here incorporate this observation into our model as reset of heterodimers, namely a resetting rule: $(l_{ft}, l_{ds}, r_{ft}, r_{ds}) = (a, b, c, d)$. We term this resetting rule *distalization* (its verb is *distalize*) in the sequel.

Divide: We make each cell divide into two. The heterodimers on the newly-created cell wall are set according to Formula (1).

Update: We update the inner heterodimers as follows:

$$\begin{cases} l_{i,\mathrm{ft}} = x_f l_{i-1,\mathrm{ft}} + y_f l_{i-1,\mathrm{ds}} + z_f r_{i+1,\mathrm{ft}} + u_f r_{i+1,\mathrm{ds}}, \\ l_{i,\mathrm{ds}} = x_d l_{i-1,\mathrm{ft}} + y_d l_{i-1,\mathrm{ds}} + z_d r_{i+1,\mathrm{ft}} + u_d r_{i+1,\mathrm{ds}}, \end{cases} \tag{2}$$

where the subscript i denotes the ith cell from the leftmost cell. We apply this update procedure once more to make the more distant heterodimers affected by each other.

The development phase is depicted in Fig. 2A.

Extract procedure is defined as a pair of numbers (e_1, e_2) that designates extraction of cells between the e_1th

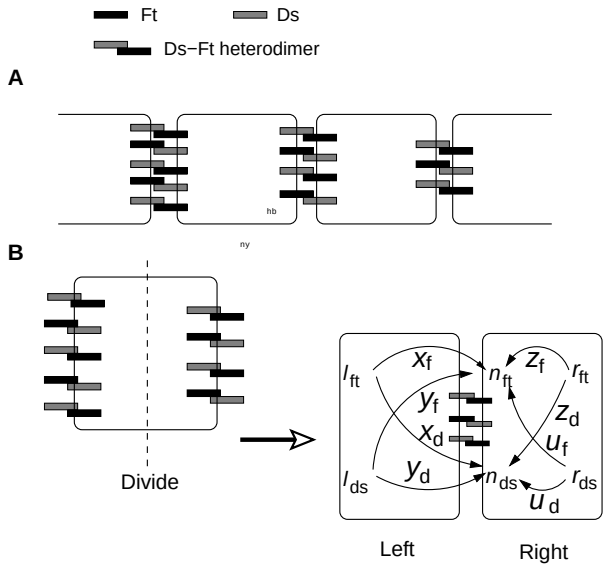

Figure 1: A schematic illustration of the Ds-Ft system. A: The heterodimeric bridges are formed by Ds and Ft molecules between cells. The gradient of Ds-Ft heterodimers across the cells is considered to provide cells with a polarity or regeneration cue [20]. B: During the cell division, surplus Ft, Ds and their heterodimers are deemed redistributed on the cell surface. $l_{\mathrm{ft,ds}}$ designates the amounts of Ft and Ds, respectively, of heterodimers on the left-side surface of the left cell. Likewise, $r_{\mathrm{ft,ds}}$ designates those on the right-side surface of the right cell, and $n_{\mathrm{ft,ds}}$ designates those on the left-side surface of the right cell. $\{x, y, z, u\}_{f,d}$ denote the redistribution ratio of heterodimers (see the text for details).

and e_2th cells. The pair $(3, 5)$, for example, designates extraction of the third to fifth cells.

Under these definitions, we constructed the **regeneration simulation** (n, p, q) as follows:

(i) Start with a single cell with both ends distalized as $(l_{\rm ft}, l_{\rm ds}, r_{\rm ft}, r_{\rm ds}) = (a, b, c, d)$.

(ii) Increase the cell number up to n through the development phase. Let C_o be the thus obtained cell chain.

(iii) Extract a part of C_o with the extract phase, (p, q). Then both ends of this part are "distalized."

(iv) Increase the cell number up to n through the development phase. Let C_e be the thus obtained cell chain.

(v) Compare C_e with C_o by measuring the difference between heterodimers of C_e and C_o. This difference is calculated as a set of polynomials:

$$\{l_{i,\rm ft} - l'_{i,\rm ft} | (1 \le i \le n)\} \cup \{l_{i,\rm ds} - l'_{i,\rm ds} | (1 \le i \le n)\}, \quad (3)$$

where l and l' are heterodimers of C_o and C_e, respectively. Notice also that $l_{i,\rm ft} = r_{i+1,\rm ds}$ and $l_{i,\rm ds} = r_{i+1,\rm ft}$ because of the (trans-)heterodimeric form.

(vi) Return Formula (3) as the output of the **regeneration simulation** (n, p, q).

The regeneration simulation is illustrated in Fig. 2B.

3. Method

We used prime ideal decomposition and Gröbner basis to analyze the output of calculation.

1. Prime ideal decomposition
   Imagine the following set of equations as an output of some simulation: $\{x^3 - 2x^2y + xy - 2y^2 - 4x + 8y = 0, 2xy - 4y^2 - 3x + 6y = 0\}$. The solution to this can be decomposed into two solutions: $\{x - 2y = 0\}$ and $\{x^2 + y = 4, 2y = 3\}$. One cannot decide x and y with the former, but can decide $x(= \pm\sqrt{5/2})$ and $y(= 3/2)$ with the latter. It is thus appropriate to perform such decomposition to analyze the system because we cannot know the decidability of solutions in advance. Such decomposition of algebraic equations is referred to as *prime ideal decomposition*, which has recently been used to analyze complicated systems [18, 26]. We here adopt prime ideal decomposition, not primary ideal decomposition because the multiplicity of roots does not matter in this model.

2. Gröbner basis and normal form
   We here used *Gröbner basis* and corresponding *normal form* so as to confirm whether or not a solution satisfies an equation. Let p be a polynomial, S be a set of polynomials, and G be a Gröbner basis of $< S >$. It then holds that if and only if the normal form of p with respect to G is zero, p can be written as $p = \sum a_i s_i (a_i :$ polynomial, $s_i \in S)$, showing that the solution to S makes p zero, that is, satisfies $p = 0$. For example, a Gröbner basis of $\{yx^2 - y^2 + 1, x - y^3 - 4\}(\equiv S_0)$ w.r.t. graded reverse lexicographic order[1] $x \succ y$ is $\{y^3 - x + 4, x^2y - y^2 + 1, x^3 - 4x^2 - xy + y^2 + 4y\}$. The normal form of $xy^4 + 4xy - y^2 + 1(\equiv p_1)$ is 0, while that of $y^6 + xy^4 + 4xy - y^2 + 1(\equiv p_2)$ is $x^2 - 8x + 16$, showing that S_0 satisfies $p_1 = 0$, but does not $p_2 = 0$. We can thus confirm whether a solution satisfies an equation without obtaining the solution of the explicit form.

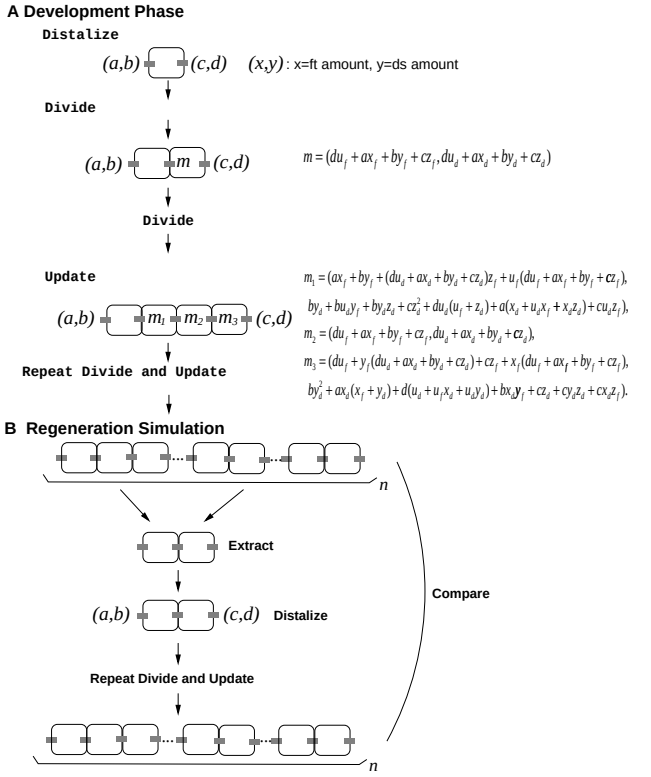

Figure 2: The development phase and the regeneration simulation. A: The Development phase. **Distalize** procedure makes each cell distalized ($(l_{ft}, l_{ds}, r_{ft}, r_{ds})$ is set (a, b, c, d) in the figure). **Divide** procedure makes each cell divide (a newly cell wall is created with heterodimers $m = (ft, ds) = (du_f + ax_f + by_f + cz_f, du_d + ax_d + by_d + cz_d)$ in the figure). **Update** procedure updates inner heterodimers (m_1, m_2, and m_3 in the figure). B: The regeneration simulation. When the cell number turns n, part of the cell chain is extracted and developed again. The cell chain thus obtained is compared with the original one (See the text.)

Let S_0 be the set of equations to analyze. In this work the complexity of S_0 was such that we first considered a subproblem S_1 of S_0. We next applied prime ideal decomposition to S_1 to find out S_1 decomposed into multiple solutions, S_{1i} $(i \ge 1)$. Using each Gröbner basis G_{1i} of S_{1i}, we surveyed which S_{1i} satisfies every element in S_0, that is, makes it zero. We thus derived a sufficient condition for the original complicated problem.

[1] The sequel holds whatever term order is used.

Here we provided a brief explanation of our method based on some issues regarding an ideal and Gröbner basis [4], which contains more precise and detailed definitions. We performed the calculation of the Gröbner basis, normal form, and prime ideal decomposition by using the routines slimgb, reduce, and minAssChar in Singular software [11].

Notice that the more variables, the more time and memory prime ideal decomposition costs, which is why we combined the two schemes above for the analysis.

4. Result

In this section we derived equations for regeneration of a cell chain even if its part is excised, according to the regeneration simulation constructed in the Model section. We aimed at derivation of equations for a 16-cell chain to regenerate even if it starts with any pair of heterodimers at both the ends and its part is excised. For this purpose, we performed sets of **regeneration simulation** for each pair in $\{(n,p,q) = (16,p,p)|1 \leq p \leq 16\} \cup \{(n,p,q) = (16,p,p+1)|1 \leq p \leq 15\} \cup \{(n,p,q) = (16,p,p+3)|1 \leq p \leq 13\}$, which means every of subcells of 1,2, and 4 length is extracted, developed, and compared with the original chain. This derivation was, however, too complicated to analyze as it stood. We hence considered a subproblem of an 8-cell **regeneration simulation** for $\{(n,p,q) = (8,p,p)|1 \leq p \leq 8\} \cup \{(n,p,q) = (8,p,p+1)|1 \leq p \leq 2\} \cup \{(n,p,q) = (8,p,p+3)|1 \leq p \leq 5\}$, which could contain a solution to the 16-cell regeneration simulation.

The 8-cell simulation started with a single cell with heterodimers $(l_{ft}, l_{ds}, r_{ft}, r_{ds}) = (a,b,c,d)$, and developed into an 8-cell chain (see also Fig. 2A). After the 8-cell chain was produced, we performed the 8-cell regeneration simulation, which yielded a condition for regeneration:

$$\begin{aligned}\{\quad & y_d(ax_d + by_d + z_d(du_d + ax_d + by_d + cz_d) + u_d(du_f \\ & + ax_f + by_f + cz_f)) + x_d(ax_f + by_f + (du_d + ax_d + \\ & by_d + cz_d)z_f + u_f(du_f + ax_f + by_f + cz_f)) + z_d(du_d \\ & + cz_d + y_d(du_d + ax_d + by_d + cz_d) + x_d(du_f + ax_f + \\ & by_f + cz_f)) + u_d(du_f + y_f(du_d + ax_d + by_d + cz_d) + \\ & cz_f + x_f(du_f + ax_f + by_f + cz_f)) - y_d(ax_d + by_d + \\ & z_d(y_d(ax_d + by_d + z_d(du_d + ax_d + by_d + cz_d) + u_d \\ & (du_f + ax_f + by_f + cz_f)) + \cdots\}. \end{aligned} \tag{4}$$

This formula consisted of 84 polynomials and had a length of about seven megabytes. We next substituted (a,b,c,d) with $(1,1,1,1)$ to obtain a solution as a specific case because we aimed to obtain a condition for any starting heterodimer (a,b,c,d). Prime ideal decomposition of this specific case of (4) was found composed of five solutions: (I) $u_f + x_f + y_f + z_f - 1 = u_d + x_d + y_d + z_d - 1 = 0$, (II) $x_f + y_d = u_f + z_f = u_d + z_d = y_f z_d - y_d z_f = y_d z_d + x_d z_f = y_d^2 + x_d y_f = 0$, (III) $x_f + y_d = u_f + z_d - 1 = z_d^2 + u_d z_f - z_d = y_f z_d - y_d z_f = y_d z_d + x_d z_f = u_d y_f - x_d z_f - y_d = y_d^2 + x_d y_f = u_d y_d - x_d z_d + x_d = 0$, (IV) $x_f + y_f = x_d + y_d = u_f + z_f = u_d + z_d = 0$, (V) $u_f + x_f + y_d + z_d - 1 = x_f z_d + y_d z_d + z_d^2 + u_d z_f - z_d = x_f y_f + y_d y_f + y_f z_d + x_f z_f - y_f = u_d y_f + y_d z_d + z_d^2 + u_d z_f - z_d = y_d^2 + x_d y_f + y_d z_d + x_d z_f - y_d = x_f y_d - x_d y_f = u_d y_d - x_d z_d = 0$.

We then surveyed which solutions satisfy Formula (4) for any (a,b,c,d) through the Gröbner basis and corresponding normal form as mentioned in the Method section. As a result, we found that only (III) above makes every element in Formula (4) zero[2].

We found out Solution (III) also satisfies the output of the regeneration simulation of $n = 16$, which formula is about three gigabytes long.

5. Discussion

We have thus far derived a condition for regeneration of the heterodimeric pattern even if its part is excised. The solution to regenerate a pattern of heterodimers is Solution (III). This solution is equivalent to the following under a condition, $y_f \neq 0$ and $z_f \neq 0$:

$$\mathbf{M}_{xy}^2 = \mathbf{M}_{uz}^2 - \mathbf{M}_{uz} = \mathbf{M}_{xy}\mathbf{M}_{uz} = \mathbf{0}, \tag{5}$$

where $\mathbf{M}_{st} = \begin{pmatrix} s_f & t_f \\ s_d & t_d \end{pmatrix}$ $(s,t \in \{x,y,z,u\})$, and $\mathbf{0} = \begin{pmatrix} 0 & 0 \\ 0 & 0 \end{pmatrix}$. This can directly be proved by ensuring the identity of the reduced Gröber bases of both the formulae, Solution (III) and (5), together with an equation $qy_f z_f - 1 = 0$ that makes $y_f = 0$ or $z_f = 0$ contradictory with an additional variable, q [3]. Indeed the Gröber basis is calculated in terms of the lexicographical order $q \succ u_d \succ u_f \succ x_d \succ x_f \succ y_d \succ y_f \succ z_d \succ z_f$ as follows:

$$\begin{aligned}\{\quad & -z_f y_d + y_f z_d, x_f + y_d, z_d y_d + x_d z_f, y_d^2 + x_d y_f, u_f + \\ & z_d - 1, z_d^2 - z_d + z_f u_d, (z_d - 1)y_d + y_f u_d, u_d y_d - x_d z_d \\ & + x_d, y_f z_f q - 1, (-y_f z_d^2 + y_f z_d)q - u_d, -y_f^2 z_d q + y_d, \\ & (-z_d^3 + 2z_d^2 - z_d)y_d q + u_d^2, y_f z_d y_d q + x_d, (-z_d^2 + z_d) \\ & y_d^2 q + x_d u_d, z_d y_d^3 q - x_d^2, (x_d z_d^4 - 3x_d z_d^3 + 3x_d z_d^2 - x_d \\ & z_d)q - u_d^3\}. \end{aligned} \tag{6}$$

Under the equations (5) (with $y_f \neq 0$ and $z_f \neq 0$), $\mathbf{M}_{xy}\mathbf{M}_{st} = \mathbf{M}_{uz}\mathbf{M}_{st} - \mathbf{M}_{st} = \mathbf{0}$ $(s \neq t, s,t \in \{x,y,z,u\})$ also holds, which can be proved likewise. These equations indicate that the left heterodimer in a cell contributes nothing to the ratio of redistribution after two updates in the development phase (see Formula (2)), while the right heterodimer allows passage through of another heterodimer pair $(s \neq t)$ as it is at the second update phase. Together with "distalization" at both the ends of a cell, these effects make the inner heterodimers fixed values, which is why the pattern is regenerated.

From these equations, we further obtain:

$$\mathbf{M}_{xy}^n \mathbf{M}_{st} = \mathbf{0},\ \mathbf{M}_{uz}^n \mathbf{M}_{st} = \mathbf{M}_{st}\ (n \geq 1, s \neq t). \tag{7}$$

In this work we performed regeneration simulations where we applied the update procedure twice in the development phase. The above formula (7) shows that the more

[2] This procedure is given in a file named "OnlineResource1.sin" at http://sites.google.com/site/codes86/files-1/.

[3] If $y_f = 0$ or $z_f = 0$, $qy_f z_f - 1 = 0$ becomes contradictory: $-1 = 0$, which enables exclusion of a condition $y_f = 0$ or $z_f = 0$.

times we apply the update procedure, the more inner heterodimers become fixed values. In fact, presupposing Solution (III), we performed regeneration simulations for $\{(n,p,q) = (32,i,i+7)|1 \leq i \leq 25\}$ and ones for $\{(n,p,q) = (32,i,i+15)|1 \leq i \leq 17\}$ with three updates, which mean regeneration from extracted eight or sixteen cells. We found out formula (5) (equivalent to Solution (III)) to be a sufficient condition for regeneration, which makes inner heterodimers fixed values together with distalization at both the ends.

We used symbolic computation to analyze the model because the output of simulations was too complicated to solve by hand. The formula (4) indeed has a length of about seven megabytes, for example, but it was found divided into five solutions of a much simpler form. The Ds-Ft heterodimer system we dealt with in this paper is related to larval denticles and the epithelium of *Drosophila* wings [17, 19, 12]. Such a system is two or three-dimensional, suggesting that expansion of our model to higher dimensional space might be promising.

6. Summary

We parameterized redistribution of Ds-Ft heterodimers during cell division, a phenomenon that is poorly understood. We derived equations to describe the relationship between parameters that allow a cell chain to regenerate its heterodimer pattern. The derived equations showed that some specific redistribution of heterodimers provides a cell chain with the ability to regenerate.

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