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Control of tissue growth by locally produced activator: Liver regeneration

Vladimir P. Zhdanov *

Section of Biological Physics, Department of Applied Physics, Chalmers University of Technology, S-41296 Göteborg, Sweden
Boreskov Institute of Catalysis, Russian Academy of Sciences, Novosibirsk 630090, Russia

HIGHLIGHTS

- The model proposed is focused on the kinetics of tissue growth.
- To motivate the model, liver regeneration is briefly discussed.
- The Hill equation is used to describe control of cell proliferation.
- Typical kinetics are shown for rapid and slow activator diffusion.
- Fits of measured kinetics of liver regeneration are shown as well.

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ABSTRACT

In general, the tissue development is controlled by growth factors and depends on the biomechanics of cells. The corresponding kinetic models are focused primarily on the early stages of the development. The attempts to construct such models for the later stages are still rare. One of the notable examples here is liver regeneration. Referring to this process, the author proposes and analyzes a generic kinetic model describing the regulation of tissue growth by locally produced activator. The model includes activator diffusion and control of the rate of cell proliferation which is described by using the Hill expression. Although this control may be moderately or strongly non-linear, the qualitative changes in the regeneration kinetics are predicted to be modest. For moderately non-linear control, the evolution of the tissue volume to the steady-state value exhibits an initial relatively short linear stage and then becomes slightly slower so that the whole kinetics is close to exponential. For strongly non-linear control, the linear stage dominates and/or the kinetics may exhibit a S-like shape feature which is, however, rather weak. The identification of such qualitative features in experimentally measured kinetics is shown to be difficult, because the error bars in the experiments are typically too large.

1. Introduction

Tissue growth is governed by various factors. The growth itself is especially important at early stages of the development. For this reason, the corresponding kinetic models are often aimed at these stages (reviewed in Refs. [1–5]). Two general concepts here are that (i) the growth or, more specifically, the fate of cells is controlled by morphogen gradients (morphogens or, in other words, growth factors are typically extracellular proteins), and (ii) this process depends on the biomechanics of

* Correspondence to: Boreskov Institute of Catalysis, Russian Academy of Sciences, Novosibirsk 630090, Russia.
E-mail address: zhdanov@catalysis.ru.

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cells. At the later stages, the control of tissue growth is often important as well. Notable examples are liver regeneration (reviewed in Refs. [6–9]), growth of tumors in general and cancer tumors in particular (the corresponding models are reviewed in Refs. [10–12]), and skin wound healing (reviewed in Refs. [13,14]; for the related kinetic models, see e.g. Ref. [15]).

The liver consists primarily of hepatocytes. After massive loss of these cells, the liver is known to have capacity for regeneration (or, in other more precise words, for compensatory hyperplasia) up to its normal size [6–9]. After e.g. surgical 70% removal (referred to as partial hepatectomy) of liver, this process occurs usually within about 2 week via proliferation and hypertrophy of hepatocytes. Mechanistically, the regeneration is influenced by increased flow of portal blood per unit of liver and consequent increased availability of all contents normally present in the portal circulation [7] and depends on various growth factors [7,8]. The important role of some of them, e.g. EGF, TGFα and HGF, was recognized many years ago [16]. One of the other key factors, for example, is now considered to be extracellular secreted glycoprotein Wnt [17]. Via binding to its cell surface receptor, Wnt regulates hepatic growth, zonation, xenobiotic metabolism and other metabolic processes inherent to the liver [17]. For human toxicity-related liver pathologies where the hepatocyte proliferation is compromised, adult liver stem/progenitor cells may become activated and differentiate to hepatocytes and cholangiocytes, leading to functional recovery of the organ [18].

Growth factors (e.g. EGF [19] and Wnt [17]) secreted by cells diffuse in interstitial fluid, bind to receptors, and induce cascades of intracellular events [20]. Their depletion occurs also via receptor binding with subsequent endocytosis and degradation [20]. The detailed understanding of where and how the growth factors are primarily produced in liver *in vivo* and how they circulate and act is still limited. In general, the area near the portal vein is often considered to be crucial for regulation of liver regeneration [8]. Recently, for example, the experiments with mice identified that the main source of Wnt appears to be Kupffer cells [21] (these cells are a subpopulation of liver sinusoidal (blood-vessel) endothelial cells [22]).

To our knowledge, the first kinetic model of liver regeneration was proposed by Bard [23,24]. In this temporal mean-field model, the inhibitor is considered to be produced in the liver and to inhibit its growth. In addition, the inhibitor is assumed to be rapidly and uniformly distributed between the liver and blood (outside the liver). The inhibitor concentration is described as

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \frac{pV}{V+W} - kc, \tag{1}$$

where p and k are the formation and degradation rate constants, V and W are the liver and blood volumes, and $V/(V+W)$ is the factor taking the inhibitor redistribution between the liver and blood into account (physically, this is the probability to find inhibitor in the liver). The equation proposed for V was

$$\frac{\mathrm{d}V}{\mathrm{d}t} = [k(c) - \kappa]V, \tag{2}$$

where $k(c)$ and κ are the liver-cell birth and death rate constants. The former rate constant was assumed to decrease with increasing c and represented as

$$k(c) = A\exp(-\alpha c), \tag{3}$$

where A and α are constants. Although activators ("wound hormones") of the liver growth were also mentioned [23], the corresponding scenario was considered to be unlikely, and the related model was not detailed.

In more recent literature, one can find a few kinetics models focused on various aspects of the liver function (see, e.g., Refs. [25–27] and review [28]). The global kinetics of liver regeneration are, however, not treated there.

According to the experiments (reviewed in Refs. [6–8]), the liver regeneration seems to be controlled by activators rather than by inhibitors. In addition, the sources of these species can be localized (e.g., near vessels). Bearing this in mind, we propose here a generic spatio-temporal model describing the control of tissue growth by locally produced activator. Using this model, we illustrate how sensitive can be the liver regeneration kinetics to the non-linear regulation of the growth of hepatocytes. Although the model was inspired primarily by the studies of liver regeneration, it or some of its ingredients can be used in other general contexts (e.g., to describe signal propagation in kidneys or tumors).

2. General equations

In our model, we operate with the liver volume, $V(t)$, which is proportional to the liver mass and related to the number of cells (hepatocytes) in the liver as

$$N(t) = V(t)/v_\circ, \tag{4}$$

where $v_\circ$ is the average cell volume. In analogy with (2), the evolution of V is determined by the birth and death of cells,

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} = \int_{V(t)} k(c(\mathbf{r},t))\mathrm{d}^3r - \kappa V(t), \tag{5}$$

where $k(c(\mathbf{r},t))$ is the birth rate constant dependent on the activator concentration, $c(\mathbf{r},t)$, κ is the death rate constant, and the integration occurs over the cell volume. Using Eq. (5), we do not pay attention to the biomechanics of cells. For liver